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SYSTEMATIC REVIEW

WILEY

# COVID-19 vaccine induced myocarditis in young males: A systematic review

Benjamin Knudsen[1] | Vinay Prasad[2]

[1]The George Washington University School of Medicine and Health Sciences, Washington, DC, USA

[2]University of California San Francisco, San Francisco, California, USA

**Correspondence**
Vinay Prasad, Department of Epidemiology and Biostatistics, UCSF Mission Bay Campus, Mission Hall: Global Health & Clinical Sciences Building, 550 16th St, 2nd Fl, San Francisco, CA 94158, USA.
Email: vinayak.prasad@ucsf.edu

## Abstract

**Background:** Myocarditis is a rare but significant adverse event associated with COVID-19 vaccination, especially for men under 40. If the risk of myocarditis is not stratified by pertinent risk factors, it may be diluted for high-risk and inflated for low-risk groups. We sought to assess how the risk of myocarditis is reported in the literature.

**Methods:** In accordance with PRISMA standards, we reviewed primary publications in PubMed, Embase, Google Scholar and MedRxiv (through 3/2022) and included studies that estimated the incidence of myocarditis/pericarditis after receiving either the BNT162b2 (Pfizer), mRNA-1273 (Moderna) or Ad26COVS1 (Janssen) vaccine. The main outcome was the percentage of studies using 4, 3, 2, 1 or 0 stratifiers (i.e. sex, age, dose number and manufacturer) when reporting the highest risk of myocarditis. Secondary outcomes included the incidence of myocarditis in males after dose 1 and 2 of the BNT162b2 (Pfizer) or mRNA-1273 (Moderna) vaccine.

**Results:** The 29 included studies originated in North America, Europe, Asia, or were Worldwide. Of them, 28% (8/29) used all four stratifiers, and 45% (13/29) used 1 or 0 stratifiers. The highest incidence of myocarditis ranged from 8.1—39 cases per 100,000 persons (or doses) in studies using four stratifiers. Six studies reported an incidence greater than 15 cases per 100,000 persons (or doses) in males aged 12–24 after dose 2 of an mRNA-based vaccine.

**Conclusions:** Only one in four articles reporting myocarditis used four stratifiers, and men younger than 40 receiving a second dose of an mRNA vaccine are at greatest risk.

**KEYWORDS**
COVID-19 vaccination, epidemiology, health policy, myocarditis

# 1 | INTRODUCTION

Myocarditis and/or pericarditis may be a serious safety signal associated with COVID-19 vaccination.[1] Early data from Israel estimated the excess risk of myocarditis from the BNT162b2 (Pfizer) vaccine to be 2.7 events per 100,000 persons across people of all demographics.[2] Since then, however, reports have emerged finding the risk of myocarditis to be much higher in certain subsets of people. In an analysis by the Centers for Disease Control (CDC) of 1626 myocarditis cases reported to the Vaccine Adverse Reporting System (VAERS) after mRNA-based COVID-19 vaccination, 1195 (73%) were younger than 30, 82% (1265/1538) occurred after the second dose and 82% (1334/1625) were males.[3] Additional published analyses have supported this data by showing that those at highest risk of myocarditis are men under age 30 who receive a second mRNA vaccine dose.[4–10]

The CDC and Food and Drug Administration (FDA) monitor COVID-19 vaccine safety which informs policy recommendations regarding the optimal vaccination schedule. In a meeting on June 7th, the CDC reported that among all demographics, adolescent men receiving the second dose of the Pfizer vaccine had the highest incidence of myocarditis.[11] The CDC has already recommended an extended delay of 3 or 4—8 weeks (from an initial recommendation of 3—4 weeks) between dose 1 and 2 of the primary mRNA COVID-19 vaccination series for healthy individuals to reduce the risk of myocarditis.[12] It is likely that they will continue to update their recommendations as more data emerges to minimise the risk and maximize the benefit of vaccination.

We performed a review of the literature to estimate the population-level incidence of myocarditis after COVID-19 vaccination. We specifically looked at studies that stratified the risk by sex, age, dose number and manufacturer to identify the subset of people at greatest risk. This information may empower policymakers and public health agencies to make prudent decisions about how to vaccinate against COVID-19 safely.

# 2 | METHODS

## 2.1 | Objective

We sought to find articles that estimate the risk of post-COVID-19 vaccine induced myocarditis broken down by sex, age, dose number and manufacturer.

The primary outcome was the percentage of studies using 4, 3, 2, 1 or 0 stratifiers (i.e. sex, age, dose number and manufacturer) when reporting the highest risk of myocarditis.

The secondary outcome was the incidence of myocarditis in men after dose 1 and 2 of the BNT162b2 (Pfizer) or mRNA-1273 (Moderna) vaccine. The Pfizer and Moderna vaccine carry the greatest risk of myocarditis. We aimed at comparing the risk of myocarditis between dose 1 and dose 2 within the same vaccine and between the two vaccines.

## 2.2 | Literature search

Articles discussing COVID-19 vaccination and myocarditis in relation to the BNT162b2 (Pfizer), mRNA-1273 (Moderna) and Ad26COVS1 (Janssen), COVID-19 vaccine was identified in PubMed, Embase, Google Scholar and MedRxiv through 3/2022 using the following general search terms: 'myocarditis', 'pericarditis', 'COVID-19 vaccine', 'BNT162b2', 'mRNA-1273', and 'Adv26' through 03/2022. The full search query can be found in the appendix (Table S1).

We limited our search to the three FDA approved or authorised COVID-19 vaccines: BNT162b2 (Pfizer), mRNA-1273 (Moderna) and Ad26COV21 (Janssen). The ChAdOx1 (AstraZeneca) vaccine was excluded because only case reports of myocarditis after vaccination were found in the literature, and some nations suspended in younger people (e.g. Germany March 2021) (Table S1).

## 2.3 | PRISMA guidelines/ article inclusion

The review article was in accordance with the standards of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement. All articles initially found were screened by a single reviewer via title/abstract, and all case reports/series, review papers and unrelated reports (i.e. myocarditis related to SARS-CoV-2 and adverse events other than myocarditis) were removed. The remaining selection was reassessed, and all reports that did not provide a population-level incidence estimate of myocarditis, pericarditis and/or myo-pericarditis were removed. Additionally, all estimates presented only as presentation, duplicates and unrelated articles were eliminated. Articles were excluded if they were not full-length original articles (i.e. >2500 words), as these often-lacked sufficient explanation of methods for categorization (Figure S1). All articles reporting an incidence risk of myocarditis/pericarditis after COVID-19 vaccination were included. A second researcher was consulted whether there was uncertainty about including a report.

## 2.4 | Data abstraction

All included articles were read completely by a single reviewer, and the following data points were extracted for the primary analysis: title, author, myocarditis risk estimates, number of stratifiers used for the highest incidence estimate, database/cohort used to derive the incidence, study country of origin, time frame postvaccination considered, myocarditis diagnosis method, journal and impact factor, accrued citations in Google Scholar and Altmetric score. The accrued citations in Google Scholar and the Altmetric score were noted on 6/6/2022 and were used to investigate the correlation between the magnitude of myocarditis risk estimates and the accrued citations in Google Scholar or Altmetric score.

The following data points were extracted, and descriptive statistics were compiled (if available in the manuscript): average age of patients with myocarditis, total number of vaccine doses administered, total number of myocarditis cases, number of myocarditis cases in males, number of myocarditis cases in females, the time frame considered and if the paper was peer reviewed and published or if it was a preprint.

The stratifiers we prespecified were: sex, age, dose number and manufacturer. These stratifiers were chosen because emerging reports suggested that the incidence of myocarditis varied among vaccine recipients of different sexes and ages, the dose received and the vaccine manufacturer. Additionally, although there are many other stratification factors to consider the ones selected were the most prevalent and were readily accessible. The time between dose 1 and 2 is another relevant stratification factor, but this was only considered in one study by Buchan et al.[10] Articles were grouped according to the number of stratifiers used to estimate the incidence of myocarditis.

In this analysis, myocarditis was considered synonymous with pericarditis and myo/pericarditis. Thus, myocarditis includes myocarditis, pericarditis and myo/pericarditis.

## 2.5 | Data analysis

Statistical analysis was performed in R version 4.2.2. The Kruskal–Wallis test was used to compare a difference in the distribution of the highest myocarditis risk by stratified groups. A univariate meta-regression was used to assess how stratification is related to the rate of myocarditis. We sought to identify if factors, such as journal impact factor, industry funding or study location, were predictors of the degree of stratify a study utilised. We used a Kruskal–Wallis test to determine whether impact factor was a predictor of the degree of stratification. The Fisher's Exact test was used to evaluate whether either industry funding or study location was a predictor of the degree of stratification.

## 2.6 | Ethics approval

In accordance with 45 CFR §46.102(f), this study was not submitted for institutional review board approval because it involved publicly available data and did not involve individual patient data.

## 3 | RESULTS

A total of 758 articles were obtained after literature search. Of those, 89% (674/758) were removed from the initial screen as they were case reports/ series, review papers or unrelated articles. Of the remaining 84 articles, 30% (25/84) were duplicates, 6% (5/84) were presentations or not full-length articles, 8% (7/84) did not provided a population-level incidence of myocarditis and 21% (18/84) were unrelated. This left 29 articles for the final analysis.

The analysis contained cases of myocarditis from males and females of all age groups. The studies came from a diverse group of countries: Hong Kong, Canada, US, Israel, UK, Denmark, South Korea, Singapore and some were worldwide.

We found 28% (eight of 29) of studies utilised four stratifiers (Table 1) and Table 2. The incidence of myocarditis ranged from 8.1 to 39 cases per 100,000 persons (or doses) when four stratifiers were examined (Figure 1). All were in men under age 40 after dose 2 of an mRNA-based vaccine.

The highest two estimates when examining four stratifiers, 39 and 37.3 cases per 100,000 persons were in males aged 12–17 after dose 2 of the Pfizer vaccine (Figure 2). The two studies reporting rates after the Moderna vaccine found a risk of 30 cases per 100,000 doses in males aged 18–24 after dose 2 and 10.1 cases per 100,000 persons in males under age 40 after dose 2 (Figure 3).

We found 17% (five of 29) of studies utilised three stratifiers (Table 1). The incidence of myocarditis ranged from 4.3 to 53.7 cases per 100,000 persons (or doses) when only three stratifiers were examined (Figure 1). The highest incidence of myocarditis across all 29 articles was found in this group. Sharff et al estimated a risk of 53.7 cases per 100,000 doses in males aged 18–24 after dose 2 of either the Pfizer or Moderna vaccine[9] (Figure 2). The lowest estimate in this group by Choe. et al, 4.3 cases per 100,000 persons, did not stratify by sex.

We noted that 10% (three of 29) of studies utilised two stratifiers (Table 1). The incidence of myocarditis ranged

**TABLE 1** Studies included in the analysis are organised by the number (not type) of stratifiers utilised (sex, age, dose number and manufacturer)

| # Of Stratifiers | Title (Author) | Highest Risk Estimate/100,000 Persons or Doses (sex; age; dose #; manufacturer) | Database or Cohort (country) | Time Frame Postvaccine Considered | Diagnosis Method (Diagnosis used) | Journal (IF) | Citations accrued as of 6/6/22 | Altmetric Score As of 6/6/22 |
|---|---|---|---|---|---|---|---|---|
| 4 Stratifiers (sex, age, dose #, manufacturer) | Myocarditis Following COVID-19 BNT162b2 Vaccination among Adolescents in Hong Kong[4] (Li, et al) | 39.02 (Male; 12–17; D2; Pfizer) | Hong Kong territory wide electronic health record database (Hong Kong) | Not reported | Inpatient cases identified via ICD-9 codes: 422.x and 429.0 (myocarditis) | JAMA Paediatrics (26.8) | 4 | 954 |
| | Epidemiology of Acute Myocarditis/Pericarditis in Hong Kong Adolescents Following Comirnaty Vaccination[5] (Chua, et al) | 37.32 (Male; 12–17; D2; Pfizer) | Hospital Authority Clinical Data Analysis and Reporting System – Hong Kong (Hong Kong) | 14d after D1 or D2 | Hong Kong Paediatric Investigation Protocol for Comirnaty-related Myocarditis/Pericarditis (Cardiovascular Injury-Coalition for Epidemic Preparedness Innovations & Brighton Collaboration Criteria) (myocarditis/pericarditis) | Oxford Academic Clinical Infectious Diseases (9.1) | 35 | n/a |
| | Epidemiology of myocarditis and pericarditis following mRNA vaccines in Ontario, Canada: by vaccine product, schedule and interval[10] (Buchan, et al) | 29.95 (Male; 18–24; D2; Moderna) | Public Health Case and Contact Management Solution—Ontario (Canada) | All reports following vaccination, regardless of time since vaccination | Brighton Collaboration Criteria level 1–3 (myocarditis/pericarditis) | medRxiv | 9 | n/a |
| | BNT162b2 Vaccine-Associated Myo/Pericarditis in Adolescents: A Stratified Risk–Benefit Analysis[6] (Krug, et al) | 16.2 (Male; 12–15; D2; Pfizer) | VAERS (US) | Not reported | CDC working definition for probably acute myocarditis (myo/pericarditis) | European Journal of Clinical Investigation (4.7) | 6 | 2180 |
| | Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel[7] (Mevorach, et al) | 15.07 (Male; 16–19; D2; Pfizer) | Ministry of Health database—Israel (Israel) | 21d after D1 or D2 | ICD-9422.0-9x and 429.0x for screening. Review by physicians and Brighton Collaboration Criteria (myocarditis) | NEJM (176) | 194 | 6640 |
| | Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021[3] (Oster, et al) | 10.59 (Male; 16–17; D2; Pfizer) | VAERS (US) | 7d after D1 or D2 | CDC case definition for probable or confirmed myocarditis and review by CDC physicians (myocarditis) | JAMA (157.3) | 104 | 9933 |

**TABLE 1** (Continued)

| # Of Stratifiers | Title (Author) | Highest Risk Estimate/100,000 Persons or Doses (sex; age; dose #; manufacturer) | Database or Cohort (country) | Time Frame Postvaccine Considered | Diagnosis Method (Diagnosis used) | Journal (IF) | Citations accrued as of 6/6/22 | Altmetric Score As of 6/6/22 |
|---|---|---|---|---|---|---|---|---|
| | Risk of myocarditis following sequential COVID-19 vaccinations by age and sex[18] (Patone, et al) | 10.1 (Male; <40; D2; Moderna) | National Data for Hospital Admission—England (UK) | 28d after D1 or D2 | ICD-10 codes: I40, I400, I401, I408, I409, I41, I410, I411, I412, I418, I514 (myocarditis) | medRxiv | 6 | n/a |
| | Myocarditis after BNT162b2 Vaccination in Israeli Adolescents[8] (Mevorach (2), et al) | 8.09 (Male; 12–15; D2; Pfizer) | Ministry of Health database—Israel (Israel) | 21d after D1 or D2 | ICD 422.0-9x and 429.0x for screening. Review by physicians and Brighton Collaboration Criteria. (myocarditis) | NEJM (176) | 13 | 664 |
| 3 Stratifiers | Risk of Myopericarditis following COVID-19 mRNA vaccination in a Large Integrated Health System: A Comparison of Completeness and Timeliness of Two Methods[9] (Sharff, et al) | 53.7 (Male; 18–24; D2; mRNA) | Kaiser Permanente Northwest (US) | 30d after D2 | ICD-10 Codes and text description of all KPNW encounters with 'myocarditis' or 'pericarditis'. (myocarditis/pericarditis) | Pharmacoepidemiology and Drug Safety (2.89) | 6 | 338 |
| | Myocarditis after Covid-19 Vaccination in a Large Health Care Organization[19] (Witberg, et al) | 10.69 (Male; 16–29; D1/2; Pfizer) | Clalit Health Services—Israel (Israel) | 21d after D1 and D2 | ICD-9 Codes: 422, 429.0, 398.0, 391.2 (and subcodes) (myocarditis) | NEJM (176) | 196 | 5271 |
| | Population-based Incidence of Myopericarditis After COVID-19 Vaccination in Danish Adolescents[20] (Nygaard, et al) | 9.7 (Male; 12–17; D1/2; Pfizer) | 18 Danish Paediatric Depts. And Danish VAERS (Denmark) | 4wks after D1 | Clinical Diagnosis (myopericarditis) | Paediatric Infectious Disease (1.7) | 12 | 360 |
| | Myocarditis After mRNA-1273 Vaccination: A Population-Based Analysis of 151 Million Vaccine Recipients Worldwide[21] (Straus, et al) | 7.40 (Male; 18–24; D1/2; Moderna) | Moderna global safety database (Worldwide) | Not reported | Brighton Collaboration; CDC working case definitions (myopericarditis) | medRxiv | 2 | n/a |
| | Safety and effectiveness of BNT162b2 mRNA Covid-19 vaccine in adolescents[22] (Choe, et al) | 4.3 (Male/Female; 16–18; D2; Pfizer) | COVID-19 Vaccination Adverse Events Management Guideline—Korea (South Korea) | 30d after D2 | COVID-19 Vaccination Adverse Events Management Guideline. Hand reported (myocarditis/pericarditis) | Vaccine (3.64) | 6 | 7 |

(Continues)

**TABLE 1** (Continued)

| # Of Stratifiers | Title (Author) | Highest Risk Estimate/100,000 Persons or Doses (sex; age; dose #; manufacturer) | Database or Cohort (country) | Time Frame Postvaccine Considered | Diagnosis Method (Diagnosis used) | Journal (IF) | Citations accrued as of 6/6/22 | Altmetric Score As of 6/6/22 |
|---|---|---|---|---|---|---|---|---|
| 2 Stratifiers | SARS-CoV-2 vaccination and myocarditis or myopericarditis: population-based cohort study[23] (Husby, et al) | 6.3 (Males; All ages; D1/2; Moderna) | Hospital-Based Diagnoses from Danish National Patient Register (Denmark) | 28d after D1 or D2 | ICD-10 codes & increased troponin & hospital stay >24hrs (myocarditis or myopericarditis) | BMJ (93.3) | 58 | 2514 |
| | Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military[24] (Montgomery, et al) | 4.36 (Male; 21–50; D2; mRNA) | US Military—Referrals to Defence Health Agency—VAERS (US) | Not reported | Adjudication process and CDC case definition (myocarditis) | JAMA Cardiology (30.15) | 298 | 4342 |
| | Carditis After COVID-19 Vaccination With a Messenger RNA Vaccine and an Inactivated Virus Vaccine: A Case–Control Study[25] (Lai, et al) | 1.00 (Male/Female; All ages; D2; Pfizer) | Hospital Authority of Hong Kong (Hong Kong) | Not reported | ICD-9-CM codes: 420.9, 422.x, 423.9, 429.0 (myocarditis/pericarditis) | Annals of Internal Medicine (51.6) | 13 | 826 |
| 1 Stratifier | Features of Inflammatory Heart Reactions Following mRNA COVID-19 Vaccination at a Global Level[26] (Chouchana, et al) | 7.82 (Male/Female; 18–29; D1/2; mRNA) | VigiBase (WHO global database of individual case safety reports) (US) | Not reported | Coded via Medical Dictionary for Regulatory Activities (myocarditis) | ASCPT (6.87) | 7 | 288 |
| | Incidence of Myopericarditis and Myocardial Injury in Coronavirus Disease 2019 Vaccinated Subjects[27] (Farahmand, et al) | 7.3 (Male; all ages; D1/2; COVID-19 Vaccine) | Beth Israel Deaconess Medical Center (US) | Not reported | ICD-10 codes: I010, I011, I012, I090, I092, I30, I31, I32, I33, I38, I39, I40, I41, I514, and I21A1 (myopericarditis) | American Journal of Cardiology (2.78) | 4 | 39 |
| | Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting[2] (Barda, et al) | 2.7 (Male/Female; All ages; D1/2; Pfizer) | Clalit Health Service (Israel) | 21d after D1 and D2 | Diagnostic codes and free-text phrases that accompany diagnoses (myocarditis) | NEJM (176) | 357 | 12,240 |
| | Myocarditis and Pericarditis following COVID-19 Vaccination: Inequalities in Age and Vaccine Types[28] (Li, et al) | 2.09 (Male/Female; 12–17; D1/2; COVID-19 Vaccines) | VAERS (US) | Not reported | Preferred terms (myocarditis, pericarditis) coded in VAERS (myocarditis/pericarditis) | Journal of Personalized Medicine (1.01) | 20 | 263 |

**TABLE 1** (Continued)

| # Of Stratifiers | Title (Author) | Highest Risk Estimate/100,000 Persons or Doses (sex; age; dose #; manufacturer) | Database or Cohort (country) | Time Frame Postvaccine Considered | Diagnosis Method (Diagnosis used) | Journal (IF) | Citations accrued as of 6/6/22 | Altmetric Score As of 6/6/22 |
|---|---|---|---|---|---|---|---|---|
| | The Safety of mRNA-1273, BNT162b2 and JNJ-78436735 COVID-19 Vaccines: Safety Monitoring for Adverse Events Using Real-World Data[29] (Sa, et al) | 0.62 (Male/Female; All ages; D1/2; Janssen) | VAERS (US) | Not reported | Not reported (myocarditis/pericarditis) | Vaccines (3.6) | 1 | n/a |
| | Acute Myocarditis Following COVID-19 mRNA Vaccination in Adults Aged 18 Years or Older[30] (Simone, et al) | 0.58 (Male/Female; >18; D2; mRNA) | Kaiser Permanente Southern California (US) | 10d after D1 or D2 | Independent review by 2 cardiologists (myocarditis) | JAMA Internal Medicine (44.41) | 42 | 1823 |
| | Safety Monitoring of mRNA Vaccines Administered During the Initial 6 Months of the U.S. COVID-19 Vaccination Program: Reports to Vaccine Adverse Events Reporting System (VAERS) and v-safe[31] (Rosenblum, et al) | 0.49 (Male/Female; All ages; D1/2; Pfizer) | VAERS & V-safe (US) | Not reported | Not reported (myopericarditis) | The Lancet Infectious Diseases (71.42) | 11 | 3126 |
| | The safety profile of COVID-19 vaccinations in the United States[32] (Singh, et al) | 0.182 (Male/Female; All ages; D1/2; Janssen) | VAERS (US) | Not reported | Not reported (myocarditis/pericarditis) | American Journal of Infection Control (3.64) | 9 | 32 |
| | Myocarditis Following COVID-19 mRNA Vaccine: A Case Series and Incidence Rate Determination[33] (Perez, et al) | 109.52/100,000 person years (Male; All ages; D1/2; mRNA) | Mayo Clinic Health System (US) | 14d after D1 or D2 | ICD-10 codes: I40.0, I40.1, I40.8, I40.9, I41, I51.4, B33.22 (myocarditis) | Oxford Academic Clinical Infectious Diseases (9.1) | 21 | 75 |
| 0 Stratifiers | Adverse reactions and safety profile of the mRNA COVID-19 vaccines among Asian military personnel[34] (Tan, et al) | 2.4 (Male/Female; All ages; D1/2; mRNA) | Singapore military personnel (Singapore) | Not reported | Hand classified by physician (myocarditis/pericarditis) | Annals Academy of Medicine, Singapore (2.47) | 1 | n/a |
| | A Small but Significantly Greater Incidence of Inflammatory Heart Disease Identified after Vaccination for Severe Acute Respiratory Syndrome Coronavirus 2[35] (Knowlton, et al) | 2.30 (Male/Female; All ages; D1/2; COVID-19 vaccines) | Intermountain Healthcare (US) | 60d after D1 | Brighton Collaboration criteria of definitive and probably myocarditis and pericarditis; Clinician review (myocarditis, pericarditis, or myopericarditis) | Oxford Academic Open Forum Infectious Diseases (3.8) | 1 | 14 |

(Continues)

**TABLE 1** (Continued)

| # Of Stratifiers | Title (Author) | Highest Risk Estimate/100,000 Persons or Doses (sex; age; dose #; manufacturer) | Database or Cohort (country) | Time Frame Postvaccine Considered | Diagnosis Method (Diagnosis used) | Journal (IF) | Citations accrued as of 6/6/22 | Altmetric Score As of 6/6/22 |
|---|---|---|---|---|---|---|---|---|
| | Myocarditis and Pericarditis After Vaccination for COVID-19[36] (Diaz, et al) | 1.0 (Male/Female; All ages; D1/2; COVID-19 Vaccine) | Providence Health Care System (US) | Not reported | Clinical diagnosis from EMR; Abnormal troponin or cardiac MRI with evidence of myocarditis. (myocarditis) | JAMA (157) | 186 | 5610 |
| | Comparisons of the risk of myopericarditis between COVID-19 patients and individuals receiving COVID-19 vaccines: a population-based study[37] (Chou, et al) | 0.55 (Male/Female; All ages; D1/2; COVID-19 Vaccine) | Hospital Authority Hong Kong West Cluster (Hong Kong) | Not reported | Expert panel review; ICD codes 420.9, 422.x, 423.9, and 429.0 (myopericarditis) | Clinical Research in Cardiology (5.46) | 1 | 50 |

*Note*: The highest population-level myocarditis risk estimate from each article is presented for simplicity. Male/Female—Male and Female. D1/2—Dose 1 and 2. mRNA—Pfizer and Moderna. COVID-19 Vaccines—Combination of multiple COVID-19 vaccines. ICD—International Disease Classification. d = days.

from 1 to 6.3 cases per 100,000 persons (or doses) when only two stratifiers were examined (Figure 1).

We found 45% (13 of 29) of studies utilised either 1 or 0 stratifiers (Table 1). The incidence of myocarditis ranged from 0.2 to 7.8 cases per 100,000 persons (or doses) when 1 and 0 stratifiers were examined (Figure 1). 85% (11 of 13) studies in this group did not separate out the risk between males from females.

The rates of myocarditis decline across groups (groups = 4, 3, 2, 1, or 0 stratifiers) using fewer stratification factors ($p = 0.0007$) (Figure 1). In other words, when myocarditis is reported more granularly, rates are highest.

The univariate meta-regression showed a significant association between the risk of myocarditis and the number of stratification factors. The comparator for the analysis was the group with 0 stratifiers. The group with four stratifiers had a beta coefficient of 2.6 ($p < 0.0001$), the group with three stratifiers had a beta coefficient of 2.4 ($p < 0.0001$), the group with two stratifiers has a beta coefficient of 0.91 ($p = 0.06$) and the group with one stratifier was not significant.

The median journal impact factor in among 4, 3, 2, 1 and 0 stratifier groups was 92.1, 3.3, 51.6, 6.9 and 4.6, respectively. The journal impact factor was not a predictor of the degree of stratification ($p = 0.257$).

Only one study was funded by industry. Industry funding was not a predictor of the degree of stratification ($p = 0.414$).

The percentage of studies conducted in the United States among 4, 3, 2, 1 and 0 stratifier groups was 50%, 11%, 67%, 20% and 75%, respectively. US or Non-US study origin was a predictor of the degree of stratification ($p = 0.02$).

The incidence of myocarditis after dose 1 of the Pfizer vaccine in men under age 40 ranged from 0.2 to 5.6 cases per 100,000 persons (or doses) (Figure 2). The incidence of myocarditis after dose 2 of the Pfizer vaccine in males under age 40 was considerably higher and ranged from 1.2 to 39 cases per 100,000 persons (or doses) (Figure 2).

The incidence of myocarditis after dose 1 of the Moderna vaccine in men under age 40 ranged from 0.5 to 3.7 cases per 100,000 persons (or doses) (Figure 3). The incidence of myocarditis after dose 2 of the Moderna vaccine in men under age 40 ranged from 2.4 to 30 cases per 100,000 persons (or doses) (Figure 3).

There were five studies with Altimetric scores greater than 5000 and Google Scholar citations greater than 100 (Table 1). Two of these studies used all four stratifiers (incidence: 15.1 and 10.6 cases per 100,000 persons (or doses)), one of the studies used three stratifiers (incidence: 10.7 cases per 100,000 persons), one of the studies used one stratifier (incidence: 2.7 cases per 100,000 persons) and one of the studies 0 stratifiers (incidence: 1.0 cases per 100,000 persons).

**TABLE 2** Descriptive statistics of all studies included in the analysis

| Descriptor | Studies using 4 stratifiers (N = 8) | Studies using 3 stratifiers (N = 5) | Studies using 2 stratifiers (N = 3) | Studies using 1 stratifier (N = 9) | Studies using 0 stratifiers (N = 4) |
|---|---|---|---|---|---|
| Average age of patients with myocarditis, median (range) | 15.25 (13.69–24) | 21.5 (16–27) | 25 | 38 (25–44) | 36 (22–48) |
| Total number of vaccine doses administered, median (range) | 9,931,875 (305,406-354,100,845) | 2,923,182 (261,334-275,252,007) | 2,800,000 | 240,000,000 (268,320-298,792,852) | 1,457,474 (127,081-7,588,200) |
| Total number of myocarditis cases, median (range) | 194.5 (13–1626) | 35 (15–1439) | 27 (23–269) | 21 (7–1956) | 31 (3–67) |
| Number of myocarditis cases in males, median (range) | 118 (12–1334) | 32.5 (13–1117) | 109.5 (23–196) | 6 (6–15) | 15 (3–15) |
| Number of myocarditis cases in females, median (range) | 18 (1–296) | 2.5 (2–292) | 36.5 (0–73) | 1 (0–6) | 5 (0–6) |
| Study Period, median weeks, (range) | 27.85 (20–38) | 31.52 (17.6–43.4) | 22.9 (17–52.7) | 31.14 (17–41.6) | 29.87 (25–33.6) |
| Full length/peer reviewed, n (%) | 6 (75) | 4 (80) | 3 (100) | 9 (100) | 4 (100) |
| Preprint, n (%) | 2 (25) | 1 (20) | 0 (0) | 0 (0) | 0 (0) |
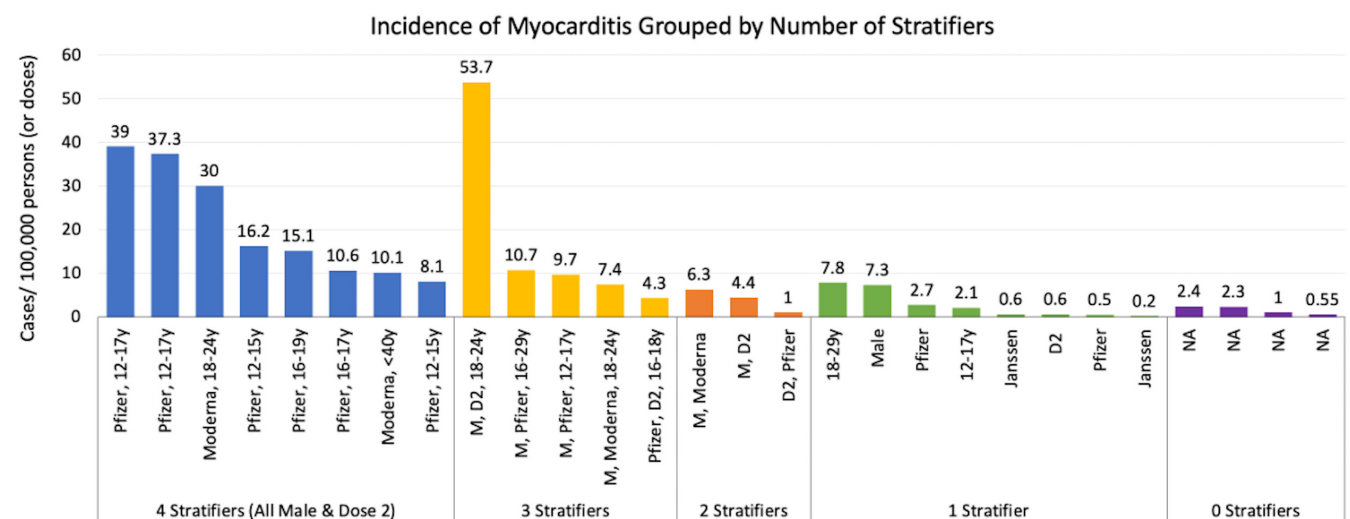


**FIGURE 1** Highest myocarditis incidence from each study. Each bar represents a unique study. Data are grouped according to the number of stratifiers used. Stratifiers are sex, age, dose number and manufacturer. Each bar is labelled on the x-axis with the stratifiers unique to the study that the estimate was obtained from. The number above each bar represents the myocarditis incidence. Male (M), Dose 2 (D2), Not Applicable (NA). In studies using four stratifiers, the stratifiers Male and Dose 2 were universally applicable

## 4 | DISCUSSION

We performed a review to identify articles that estimated the incidence of COVID-19 vaccine induced myocarditis in young males. Our analysis was broad which identified both published and unpublished literature. We found 29 articles that met the inclusion criteria and categorised them based on how the incidence of myocarditis was reported.

Overall, we found that higher incidences of myocarditis were correlated with more granular data. In other words, studies that stratified by all four (sex, age, dose number and manufacturer) or even three risk factors reported the highest rates of myocarditis, with few exceptions. This was supported by the univariate meta-regression which showed a significant association between the degree of stratification and the myocarditis risk. In studies that did not stratify appropriately, the risk estimate is likely diluted for subgroups of people at higher risk (young men) and inflated for people at lower risk (older women). In an era of precision medicine, it seems inappropriate to use a nonstratified or
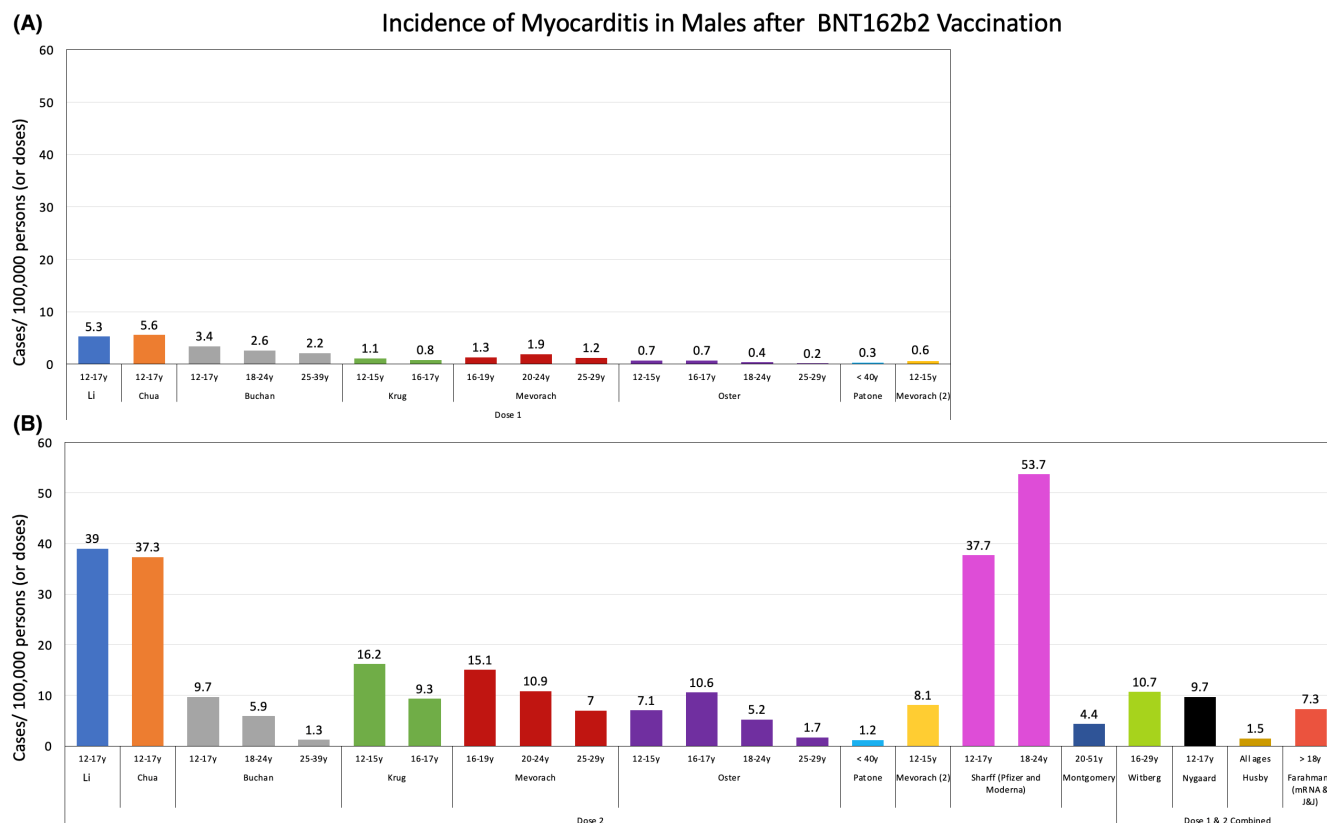
**FIGURE 2** Myocarditis incidence in males after of BNT162b2 (Pfizer) vaccination. (A) Incidence of myocarditis after dose 1 of BNT162b2 vaccination. (B) Incidence of myocarditis after dose 2 (left) or after either dose 1 or 2 (right) of BNT162b2 vaccination. Sharff et al is an exception and combines data from Pfizer and Moderna vaccination. Estimates are grouped by the study they were collected from—indicated by the author listed on the x-axis. Bars of the same colour are estimates from the same study but from a different age group. Incidence estimates were only included from studies that separated men from women and provided an estimate of the incidence of myocarditis in males after BNT162b2 vaccination

broad myocarditis incidence estimates when forming policy around vaccinating young men, a category easily identifiable.

Consistently, we found that men under the age of 40 who received a second dose of either the Pfizer or Moderna vaccine had the highest incidence of myocarditis. Our review covered the time of the initial vaccine roll-out and the months that followed. During this period, adverse events associated with COVID-19 vaccination, such as myocarditis, were first being identified. Given that as high as 70% of studies reporting adverse events associated with COVID-19 vaccination did not stratify enough to calculate the incidence in the demographic at highest risk, public health officials may have overlooked or minimised this complication, delaying the opportunity for risk mitigation.

Our analysis showed higher rates of myocarditis than reported by the CDC through the Vaccine Adverse Events Reporting System (VAERS). As of a 7 June 2022, presentation, VAERS documented 4.64 cases per 100,000 doses for those aged 12–15 and 7.59 cases per 100,000 doses for those aged 16–17 after dose 2 of the Pfizer vaccine.[11] However, data from Vaccine Safety Datalink (VSD) aligns

better with our report. Vaccine Safety Datalink reports 15.3 cases per 100,000 doses for those aged 12–15 and 13.9 cases per 100,000 doses for those aged 16–17 after dose 2 of the Pfizer vaccine.[11] Notably, Sharff et al found that VSD undercounts cases of myocarditis. Her analysis using encounter text description keyword searching identified five additional cases of myocarditis that were missed using VSD methodology.[9]

Furthermore, we found that for both Pfizer and Moderna vaccines, the risk of myocarditis is orders of magnitude greater after the second dose compared to the first dose, especially for age groups under 25. There are five studies reporting an incidence greater than 10 cases per 100,000 persons (or doses) in men aged 12–19 after dose 2 of the Pfizer vaccine. The risk of myocarditis across those five studies ranges from 1/2562 to 1/9442 persons. The Moderna COVID-19 vaccine was approved later than Pfizer's; thus, there are less data on the incidence of myocarditis. However, we found that men aged <40 who receive the second dose are at highest risk.

To contextualise the incidence of myocarditis after COVID-19 vaccination, it is helpful to compare the risk to

**FIGURE 3** Myocarditis incidence estimates in males after mRNA-1273 (Moderna) vaccination. (A) Incidence of myocarditis after dose 1 of mRNA-1273 vaccination. (B) Incidence of myocarditis after dose 2 (left) or after either dose 1 or 2 (right) of mRNA-1273 vaccination. Estimates are grouped by the study they were collected from—indicated by the author listed on the x-axis. Bars of the same colour are estimates from the same study but from a different age group. Incidence estimates were only included from studies that separated males from females and provided an estimate of the incidence of myocarditis in men after mRNA-1273 vaccination
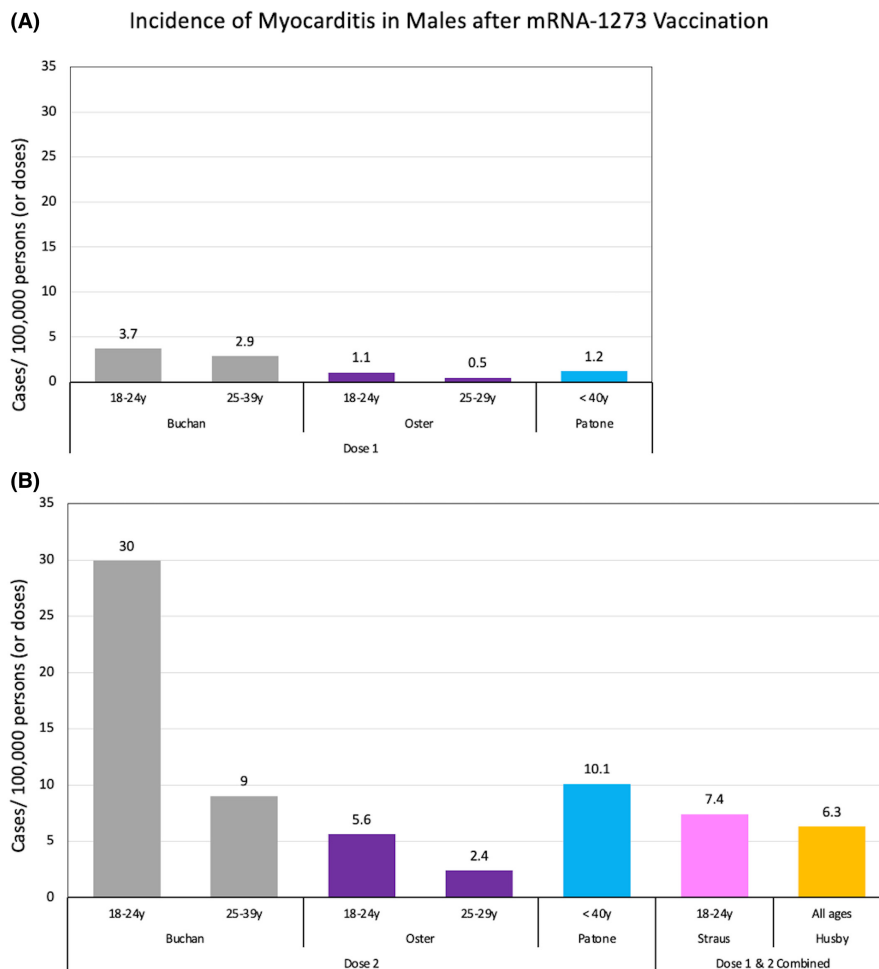
the incidence of myocarditis after influenza vaccination or SARS-CoV-2 infection. Myocarditis is typically not associated with influenza vaccination; thus, there are few, if any reports describing the incidence. On the contrary, myocarditis is a known cardiovascular sequala of COVID-19.[13] The CDC estimated that among men 12–17 and 18–29, the incidence of myocarditis and myocarditis or pericarditis was 50.1–64.9 and 55.3–100.6 cases per 100,000, respectively.[13] The incidence of myocarditis found for young men after SARS-CoV-2 infection is larger than what we found for myocarditis following COVID-19 vaccination. Moreover, Patone et al showed that the number of excess myocarditis events after SARS-CoV-2 infection was at least four times larger than after either dose 1 or 2 of the AstraZeneca, Pfizer or Moderna vaccine among people of all ages.[14] However, when Patone's analysis was limited to those under 40, the number of excess myocarditis events after dose 2 of the Moderna vaccine outnumbered those having had a SARS-CoV-2 infection.[14] Furthermore, calculating the incidence of myocarditis after vaccination is relatively precise given that the two inputs, cases of myocarditis and vaccine doses administered, are known. The calculation for estimating the incidence of myocarditis after SARS-CoV-2 infection is more challenging to obtain

because the total number of people who have had an infection is likely unknown and unattainable. Studies typically rely on documented infections, which likely suffers the flaw of undercounting the total number of infections because not everyone with the infection has a documented positive test. Thus, the incidence may be inflated and inaccurate. Using seroprevalence data as opposed to documented infections would better capture the total number of infections in a given population, and would more accurately estimate myocarditis post infection.

There is variability between the rates of myocarditis across studies, even within the same stratifying bin. This is likely due to multiple factors. One being the time-frame postvaccine dedicated to capturing adverse events is not uniform across all studies (Table 1). Some have wider windows than others, which affects the number of myocarditis cases attributed to vaccination. Additionally, across studies, there was variability between the diagnostic criteria used to evaluate whether a patient was experiencing myocarditis (Table 1). Some criteria may be more strict or lenient leading to less or more cases of myocarditis meeting inclusion, respectively. Finally, we included studies performed in multiple countries and across various health systems or databases dedicated to recording

adverse events attributed to vaccination. There is inherent variability between the collection methods used by each system. For example, some use active surveillance while others use passive recording. We acknowledge that the pitfalls in uniformity make myocarditis incidence estimates less certain; however, the available data are still valuable and helps distil who is at greatest risk.

We did not find a correlation between the magnitude of myocarditis risk estimates and either the accrued citations in Google Scholar or the Altmetric score. The accrued citations in Google Scholar and the Altmetric score are both crude and early estimates of the publicity an article receives. The number of citations or Altmetric score was more correlated with the prestige of the journal publishing the article than the myocarditis risk estimate.

We attempted to identify characteristics of either the study or the journal that would correlate with the degree of stratification utilised by a particular study. We found that impact factor and industry funding was not significantly associated with the degree of stratification. However, we did find that the country origin of either US or non-US was significantly associated with the degree of stratification.

## 4.1 | Strengths and limitations

This study has at least two strengths and four limitations. To our knowledge, ours is the largest and most comprehensive review on this topic. Previous systematic reviews on adverse events associated with COVID-19 vaccination focus on describing the clinical course and outcomes of vaccine induced injury gathered from case reports or series[15,16,17] or limit their analysis to reports from vaccine safety surveillance databases.[17] Rather than describing clinical sequalae, ours is the first to summarise the predicted incidence of postvaccine myocarditis across unpublished and published literature. We are also the first to document the phenomenon where the number of stratification factors by which myocarditis is reported correlates with aggregate risk results. Yet, we have four limitations. Since our initial literature search (03/2022), additional data have been collected and published on the incidence of postvaccine myocarditis. Our manuscript does not include these reports, but on crude observation, the new estimates agree with the data presented here. Second, we did not score each study according to its quality of data and therefore viewed each study equally. If a study utilised poor data, we did not account for this in our analysis. Additionally, our analysis is limited by the data presented in each study. For example, we were not able to present myocarditis incidence estimates in young men from studies that did not stratify data by sex and age. Finally, due to heterogeneity of data sources, definitions and lack of

complete stratification, we did not pursue meta-analytic or pooled estimate, and merely chose to describe our results. Pooled estimates would suffer from missing data.

## 5 | CONCLUSION

Myocarditis is a serious adverse event that disproportionately affects men under 40, with highest risk among men aged 12–24 who receive a second dose of a COVID-19 mRNA vaccine. We show that when investigators present the risk of myocarditis stratified by sex, age, dose number and manufacturer, it is much larger than without stratification. An important safety signal may have been ignored or minimised by failure to stratify appropriately.

## ORCID
*Benjamin Knudsen* https://orcid.org/0000-0002-9709-3076
*Vinay Prasad* https://orcid.org/0000-0002-6110-8221

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Reference 68.

Mansanguan S, Charunwatthana P, Piyaphanee W, Dechkhajorn W, Poolcharoen A, Mansanguan C. Cardiovascular Manifestation of the BNT162b2 mRNA COVID-19 Vaccine in Adolescents. Trop Med Infect Dis [Internet]. 2022 Aug 19;7(8). Available from: http://dx.doi.org/10.3390/tropicalmed7080196

*Article*

# Cardiovascular Manifestation of the BNT162b2 mRNA COVID-19 Vaccine in Adolescents

**Suyanee Mansanguan [1], Prakaykaew Charunwatthana [2], Watcharapong Piyaphanee [2], Wilanee Dechkhajorn [3], Akkapon Poolcharoen [4] and Chayasin Mansanguan [2,*]**

[1] Bhumibol Adulyadej Hospital, Bangkok 10220, Thailand
[2] Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand
[3] Department of Tropical Pathology, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand
[4] Samitivej Srinakarin Hospital, Bangkok 10250, Thailand
* Correspondence: chayasin.man@mahidol.ac.th

**Abstract:** This study focuses on cardiovascular manifestation, particularly myocarditis and pericarditis events, after BNT162b2 mRNA COVID-19 vaccine injection in Thai adolescents. This prospective cohort study enrolled students aged 13–18 years from two schools, who received the second dose of the BNT162b2 mRNA COVID-19 vaccine. Data including demographics, symptoms, vital signs, ECG, echocardiography, and cardiac enzymes were collected at baseline, Day 3, Day 7, and Day 14 (optional) using case record forms. We enrolled 314 participants; of these, 13 participants were lost to follow-up, leaving 301 participants for analysis. The most common cardiovascular signs and symptoms were tachycardia (7.64%), shortness of breath (6.64%), palpitation (4.32%), chest pain (4.32%), and hypertension (3.99%). One participant could have more than one sign and/or symptom. Seven participants (2.33%) exhibited at least one elevated cardiac biomarker or positive lab assessments. Cardiovascular manifestations were found in 29.24% of patients, ranging from tachycardia or palpitation to myopericarditis. Myopericarditis was confirmed in one patient after vaccination. Two patients had suspected pericarditis and four patients had suspected subclinical myocarditis. In conclusion, Cardiovascular manifestation in adolescents after BNT162b2 mRNA COVID-19 vaccination included tachycardia, palpitation, and myopericarditis. The clinical presentation of myopericarditis after vaccination was usually mild and temporary, with all cases fully recovering within 14 days. Hence, adolescents receiving mRNA vaccines should be monitored for cardiovascular side effects. Clinical Trial Registration: NCT05288231.

**Keywords:** BNT162b2 mRNA COVID-19 vaccine; COVID-19 vaccine; cardiovascular manifestation; myocarditis; adolescents; Thailand

## 1. Introduction

In December 2020, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the Pfizer–BioNTech mRNA vaccine (BNT162b2) for the prevention of COVID-19 disease. Clinical trials have revealed that the vaccine's efficacy is 95% and its safety profile is good, similar to that of other vaccines [1–4]. Systemic reactions to the vaccine, which were usually mild and transient, have been reported more commonly among the younger population and more often after the second dose [1,2,5].

Historically, post-vaccination myocarditis has been reported as a rare adverse event after vaccinations, especially smallpox [4], influenza, and hepatitis B vaccination, among others. In the general population, myocarditis is diagnosed in approximately 10–20 individuals per 100,000 per year [6], and occurs more commonly and at younger ages in males than females [7]. The highest reported incidence of myocarditis from vaccination occurred after a second dose of mRNA COVID-19 vaccine, and mostly among young men [8–10].

Most of these cases developed symptoms within the first week, typically 2–4 days post-vaccination. The prognosis for myocarditis patients varies according to etiology [11]. In the pre-COVID-19 era (1990–2018), among 620,195 reports filed in the Vaccine Adverse Event Reporting System (VAERS), 0.1% were attributable to myopericarditis; of these myopericarditis reports, 79% were in males [12]. However, the VAERS is primarily a safety signal detection and hypothesis-generating system, and cannot be used to determine whether the vaccine caused the adverse events [13]. Cardiovascular findings from mRNA COVID-19 vaccine included myocardial injury (myocarditis), coronary heart disease, heart failure, hypertension, and rhythm disorder [13]. The cardiovascular manifestations of COVID-19 infection include elevated cardiac biomarkers, myocarditis, cardiac arrhythmia, and venous thromboembolism [14].

Recently, a Centers for Disease Control and Prevention (CDC) advisory committee on immunization practices identified a likely association between the two COVID-19 mRNA vaccines from Pfizer–BioNTech and Moderna, and cases of myocarditis and pericarditis [15–17]. For the cardiovascular system, 4863 adverse events were reported among patients who received the BNT162b2 mRNA COVID-19 vaccine. Common findings observed with vaccines under study were tachycardia (16.41%), flushing (12.17%), increased heart rate (9.03%), hypertension (5.82%), and hypotension (3.6%) [13]. Although cardiovascular events have been reported with the COVID-19 vaccine, causality has yet to be established, because such cardiovascular adverse events are also common among the general public who do not receive the intervention [13]. Conducted during the implementation of the national Thai vaccination campaigns for adolescents, this study sought to characterize, classify, and evaluate the dynamics of cardiac function and electrocardiographic (ECG) abnormalities post-BNT162b2 mRNA COVID-19 vaccination to understand and identify cardiovascular effects that may predict cardiac complication by serial echocardiographic studies, ECG, and cardiac biomarkers for the early detection of subclinical myocarditis cases.

## 2. Materials and Methods

### 2.1. Study Design

This prospective cohort study focused on adolescent students from Kong Thabbok Upatham Changkol Kho So Tho Bo School and Wachirathamsatit School who received a second dose of the BNT162b2 mRNA COVID-19 vaccine. The study included subjects who were: (1) aged 13–18 years; (2) male or female; and (3) had received the first dose of the BNT162b2 mRNA COVID-19 vaccine without serious adverse event. Patients who had a history of cardiomyopathy, tuberculous pericarditis or constrictive pericarditis, and severe allergic reaction to the COVID-19 vaccine were excluded from the study. Laboratory tests included cardiac biomarkers (troponin-T, creatine kinase-myocardial band (CK-MB)), ECG, and echocardiography at three clinical visits (baseline, Day 3, Day 7, and Day 14 (optional for subjects with cardiac manifestation)) after receiving the second dose of the BNT162b2 mRNA COVID-19 vaccine. Participant data, including demographic data, clinical presentation, and laboratory findings, were recorded in a pre-defined case record form.

Potential subjects at Kong Thabbok Upatham Changkol Kho So Tho Bo School and Wachirathamsatit School were informed about the study by invitation letter, followed by an online meeting for parents and students to consider enrollment in the study. Informed consent documents were provided for interested parents to bring to the team investigator at enrollment. Enrollment was conducted from 3 November to 7 December 2021.

### 2.2. Diary Card

All participants received a diary card to record cardiac symptoms, such as chest pain or palpitations. Participants who developed cardiovascular effects or side effects from the vaccine could telephone the principal investigator and be transferred by phone to the medical team at the Hospital for Tropical Diseases for assessment. If the participant

developed abnormal ECG, echocardiographic findings, or increased cardiac enzymes, the principal investigator scheduled patients for follow-up per protocol and for Day 14 lab assessments.

### 2.3. Definition of Cardiovascular Manifestation

In this study, cardiovascular manifestation was defined as one or more of the following:
1.   Chest pain/pericarditis
2.   Dyspnea/orthopnea
3.   Palpitation
4.   Hypertension/hypotension
5.   Tachycardia/bradycardia
6.   Shock/cardiogenic shock
7.   Abnormal ECG or abnormal rhythm or ECG change
8.   Bundle branch block
9.   Decreased ejection fraction
10.  Diastolic dysfunction
11.  Elevation in at least one cardiac biomarker (troponin-T, CK-MB)/myocarditis

### 2.4. Definition of Myocarditis [18]

The diagnostic criteria for myocarditis were classified as either probable cases or confirmed cases. Myocarditis patients were those with the presence or worsening of more than one of the following clinical symptoms along with evidence of inflammation: (1) chest pain, pressure, or discomfort; (2) dyspnea, shortness of breath, or pain with breathing; (3) palpitation; or (4) syncope and more than one new finding of: (a) troponin level above upper normal limit of normal; (b) abnormal ECG or rhythm monitoring consistent with myocarditis; (c) abnormal cardiac function or wall motion on echocardiography; (d) cardiac magnetic resonance imaging (cMRI) findings consistent with myocarditis and no identifiable cause for symptoms and findings.

### 2.5. Definition of Pericarditis [18]

The diagnostic criteria for pericarditis included the new presence or worsening of more than two of the following clinical features: (1) acute chest pain; (2) pericardial rub on exam; (3) new ST-segment elevation or PR-segment depression on ECG; and (4) pericardial effusion on echocardiography or cMRI.

### 2.6. Cardiac Enzymes

High-sensitivity cardiac troponin-T assay (HS-cTnT) and CK-MB isoenzyme levels were determined for all participants at baseline, and on Day 3, Day 7, and Day 14 (optional) after the second vaccination dose. HS-cTnT was measured using the Elecsys troponin-T hs assay (Roche Diagnostics, Mannheim, Germany); serum levels > 14 ng/L were considered elevated. CK-MB was also measured by electrochemiluminescence immunoassay with Elecsys CK-MB (Roche Diagnostics, Mannheim, Germany); serum CK-MB levels > 6.22 ng/mL in males and >4.88 ng/mL in females were considered elevated. CRP levels > 5 mg/L were considered elevated. ESR > 20 mm/h was considered elevated. All tests during the study were performed by hospital technicians.

### 2.7. Echocardiography Protocol

Echocardiograms during the examination were recorded using the Vivid E9 ultrasound platform (GE Healthcare, Chicago, IL, USA). All echocardiographic images were recorded and reviewed by two cardiologists. Routine two-dimensional echocardiograms and color-flow Doppler images were obtained in the standard parasternal long axis view, subcostal view, and apical four-chamber views. The left ventricular walls and dimensions were measured in accordance with the guidelines of the American Society of Cardiology.

Transmitral pulsed-wave Doppler velocities (peak E- and A-wave velocities) were measured in the apical four-chamber view with the sample volume positioned at the mitral valve.

Pericardial effusion and other anatomical and functional findings were recorded when present. Echocardiographic studies were performed at baseline, and on Day 3, Day 7, and Day 14 (optional) after the second BNT162b2 mRNA COVID-19 vaccine dose.

### 2.8. Sample Size Calculation

To calculate estimated sample size, we used the estimated prevalence described in a previous study, where the incidence of cardiac manifestation among patients who received COVID-19 vaccine was found to be 4.6% [19]. Based on a population size of 1000 students after the first BNT162b2 mRNA COVID-19 vaccine dose, a minimum sample size of 297 was calculated to be sufficient for this study to determine cardiovascular effects, with an error of 2% at a 95% confidence interval. We expected that 5% of patients could be lost to follow-up or drop out before study end.

### 2.9. Statistical Analysis

All data were analyzed using SPSS version 18 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized and expressed as frequencies and percentages. Quantitative variables were presented as mean $\pm$ SD. The chi-square test or Fisher's exact test was used to assess differences between groups, as appropriate. For all analyses, $p < 0.05$ was considered statistically significant.

## 3. Results

A total of 314 participants were enrolled into the study; 13 of these were excluded from analysis, being lost to follow-up. The remaining 301 participants in the study made up the analysis set, as shown in Figure 1.

### 3.1. Characteristics of the Study Population

The mean age of the participants was 15 years (standard deviation (SD) 1.6 years; range 13–18 years). Of the 301 participants, 202 (67.1%) were male. All participants were healthy and without any abnormal symptoms before receiving the second dose of vaccine. The majority of the participants (257/301, 85.38%) had no underlying diseases. There were 44 participants with underlying medical conditions, including allergic rhinitis, asthma, thalassemia trait, and G6PD deficiency. There was no significant difference in clinical characteristics between the 13–15-year-old group and the older adolescents in this study cohort. The clinical characteristics of all 301 participants are shown in Table 1.

During the follow-up period, after receiving the second dose of vaccine, two patients were hospitalized and one patient was supervised in the ICU during hospitalization, mainly for observation of arrhythmia. The mean length of stay in the hospital was 4.5 days (range 2–7). None of the participants died, required mechanical ventilation, or required inotropic support.

### 3.2. Cardiovascular Findings

Cardiovascular adverse events observed during the study were tachycardia (7.64%), shortness of breath (6.64%), palpitation (4.32%), chest pain (4.32%), and hypertension (3.99%). Fifty-four patients had abnormal electrocardiograms (predominantly sinus tachycardia or sinus arrhythmia) after vaccination. All 54 of these patients had normal left ventricular ejection fraction. Three patients had minimal pericardial effusion. The cMRI revealed findings compatible with subacute myopericarditis (no evidence of myocardial edema with evidence of nonischemic delayed enhancement at lateral wall and pericardial enhancement at inferolateral wall) in one patient who was diagnosed with myopericarditis, as shown in Figure 2A–C. In addition, follow-up cMRI 5 months later showed no evidence of myocardial edema, myocardial delayed enhancement, or myocardial fibrosis. There is evidence of resolved myocarditis, as shown in Figure 2D–F. Incidental findings

on echocardiography included a bicuspid aortic valve and a dilated coronary sinus from persistent left superior vena cava. Six patients had mitral valve prolapse, and six patients had hypertension (HTN). Three patients diagnosed with myopericarditis and pericarditis were treated with nonsteroidal anti-inflammatory drugs (NSAIDs) for 2 weeks with no residual symptoms and complete follow-up. The patients presenting with myopericarditis, subclinical myocarditis, and pericarditis are shown in Table 2.
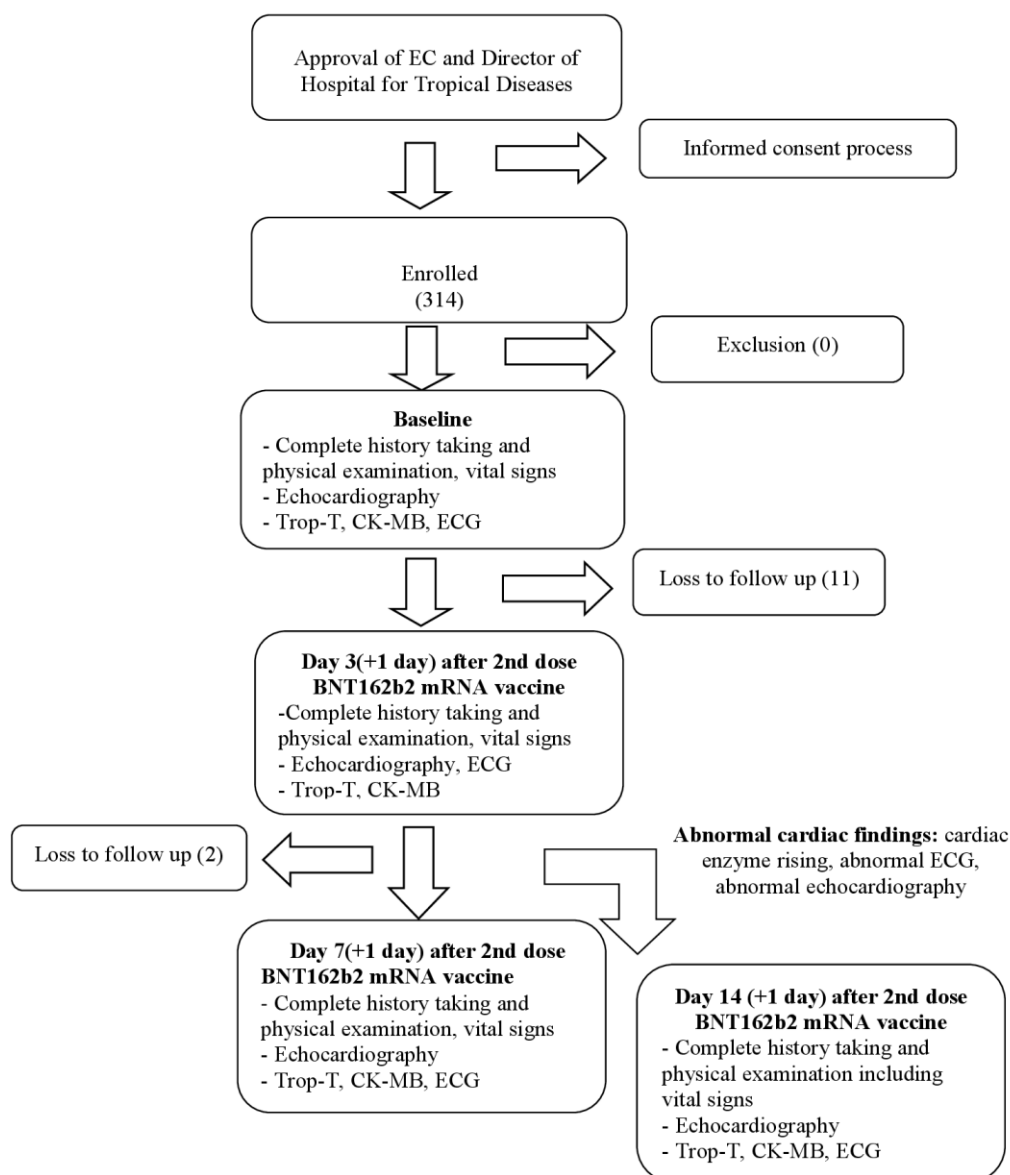
**Figure 1.** Study flow chart. CK-MB, creatine kinase-myocardial band; ECG, electrocardiography; Trop-T, troponin-T.

**Table 1.** Clinical characteristics of the 301 adolescents after the second COVID-19 vaccination.

| Characteristic | Overall (*n* = 301) | 13–15 y (*n* = 207) | 16–18 y (*n* = 94) | *p*-Value |
|---|---|---|---|---|
| Age, y | 15 ± 1.6 | 14 ± 0.8 | 17 ± 0.7 | - |
| BMI (kg/m$^2$) | 21 ± 5.0 | 20 ± 4.8 | 22 ± 5.2 | 0.017 |
| Male sex, *n* (%) | 202 (67.1) | 110 (53.1) | 92 (97.9) | <0.0001 * |
| Underlying disease *n* (%) | 44 (14.6) | 31 (15.0) | 13 (13.8) | 0.795 |

**Table 1.** *Cont.*

| Characteristic | Overall (*n* = 301) | 13–15 y (*n* = 207) | 16–18 y (*n* = 94) | *p*-Value |
|---|---|---|---|---|
| Allergic rhinitis | 24 (8.0) | 17 (8.2) | 7 (7.4) | 0.813 |
| Asthma | 7 (2.3) | 5 (2.4) | 2 (2.1) | 0.869 |
| Thalassemia trait | 5 (1.7) | 3 (1.4) | 2 (2.1) | 0.688 |
| G6PD deficiency | 4 (1.3) | 3 (1.4) | 1 (1.1) | 0.782 |
| Attention deficit | 1 (0.3) | 1 (0.5) | 0 | 0.500 |
| Epilepsy | 1 (0.3) | 1 (0.5) | 0 | 0.500 |
| Migraine | 1 (0.3) | 1 (0.5) | 0 | 0.500 |
| Thyrotoxicosis | 1 (0.3) | 0 | 1 (1.1) | 0.500 |
| Symptoms, *n* (%) | | | | |
| Fever | 50 (16.6) | 30 (14.5) | 20 (21.3) | 0.093 |
| Palpitation | 12 (4.0) | 10 (4.8) | 2 (2.1) | 0.268 |
| Chest pain | 8 (2.7) | 5 (2.4) | 3 (3.2) | 0.699 |
| Shortness of breath | 19 (6.3) | 16 (7.7) | 3 (3.2) | 0.134 |
| Headache | 35 (11.6) | 27 (13.0) | 8 (8.5) | 0.257 |
| Laboratory findings | | | | |
| Troponin-T, ng/L | $5.6 \pm 2.5$ | $5.4 \pm 2.5$ | $5.9 \pm 2.5$ | 0.112 |
| CK-MB ng/mL | $1.4 \pm 0.9$ | $1.4 \pm 0.9$ | $1.5 \pm 0.9$ | 0.473 |
| Treatment and hospital course | | | | |
| NSAIDS, *n* (%) | 3 (1.0) | 1 (0.5) | 2 (2.1) | 0.178 |
| Hospitalization, *n* (%) | 2 (0.7) | 0 | 2 (2.1) | 0.035 |
| ICU admission, *n* (%) | 1 (0.3) | 0 | 1 (1.1) | 0.138 |

* Statistically significant (chi-square test). BMI, body mass index; CK-MB, creatine kinase-myocardial band; NSAIDS, nonsteroidal anti-inflammatory drugs; Trop-T, Troponin-T.
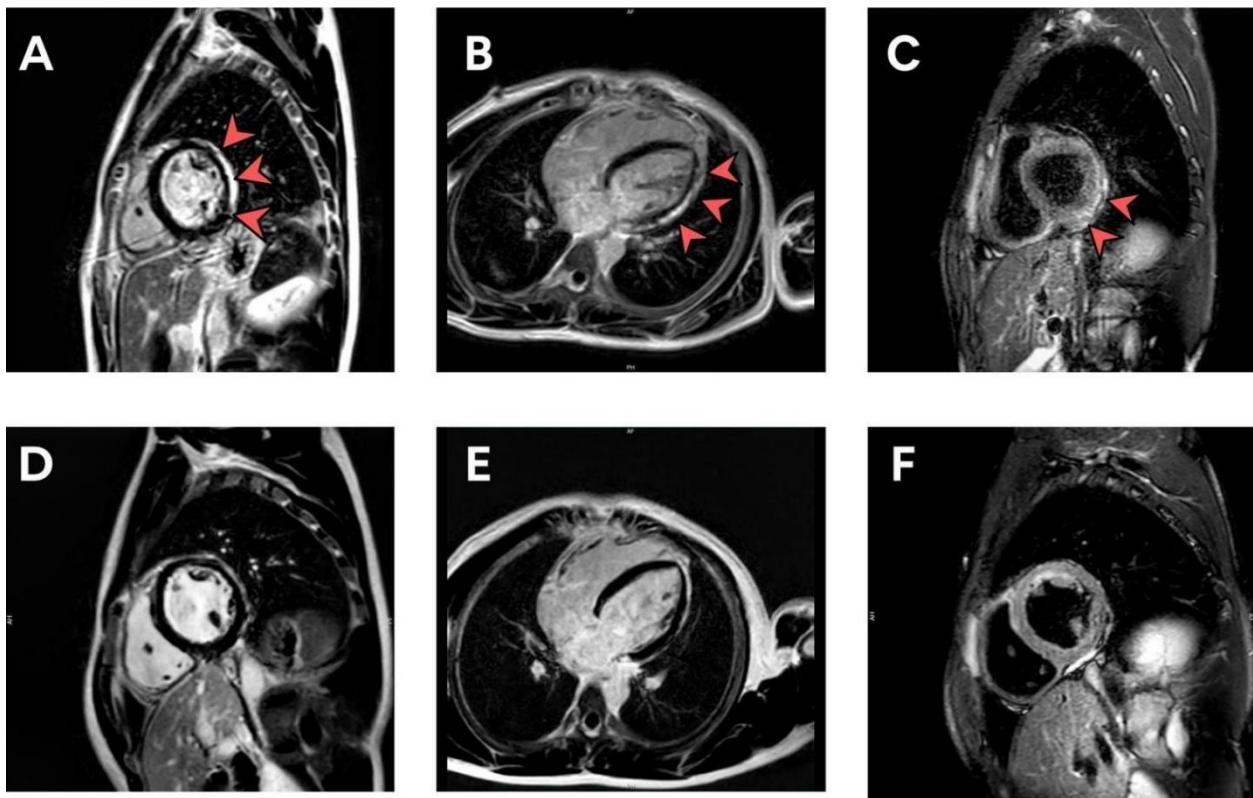


**Figure 2.** (**A–F**) cMRI illustrating LGE in a patient with subacute myopericarditis at the time of diagnosis (**A–C**) and 5 months post-diagnosis (**D–F**). cMRI, cardiac magnetic resonance imaging; LGE, late gadolinium enhancement.

**Table 2.** Presentation with myopericarditis, subclinical myocarditis, and pericarditis after second dose vaccination.

| Variable | Value |
|---|---|
| **Presenting symptoms and signs—Number/total number (%)** | |
| Chest pain | 3/7 (42.86) |
| Chest discomfort | 3/7 (42.86) |
| Pericardial effusion | 3/7 (42.86) |
| Fever | 4/7 (57.14) |
| Headache | 2/7 (28.57) |
| Palpitation | 1/7 (14.29) |
| Dyspnea | 1/7 (14.29) |
| **Vital signs on day of symptoms (Mean ± SD)** | |
| Temperature—°C | 36.4 ± 0.4 |
| Blood pressure—mmHg | |
| Systolic | 114.9 ± 10.9 |
| Diastolic | 70.7 ± 7.8 |
| Heart rate—beats/min | 92.71 ± 21.3 |
| Shock-Number/total number. (%) | 0/7 (0) |
| **Electrocardiographic findings—Number/total number (%)** | |
| Normal sinus rhythm | 1/7 (14.29) |
| Sinus rhythm with sinus arrhythmia | 2/7 (28.57) |
| Diffuse ST elevation with PR depression | 1/7 (14.29) |
| Sinus arrhythmia with PAC | 1/7 (14.29) |
| Sinus tachycardia | 1/7 (14.29) |
| Junctional escape rhythm | 1/7 (14.29) |
| **Laboratory values** | |
| Elevated troponin-T | 5/7 (71.43) |
| **Clinical course** | |
| Arrhythmia | 4/7 (57.14) |
| ICU admission | 1/7 (14.29) |
| Need for inotrope or vasopressor | 0/7 (0) |
| Death | 0/7 (0) |
| **Treatment and hospital course** | |
| Ibuprofen (NSAIDs) | 3/7 (42.86) |

Data are reported as percentage (%) and means ± standard deviations; °C, degree Celsius; NSAIDs, nonsteroidal anti-inflammatory drugs; PAC, premature atrial contraction.

### 3.3. Evaluation of Patients with Elevated Biomarkers or Positive Lab Assessments

Seven patients had elevated biomarkers or positive lab assessments. The most commonly presented symptom was chest pain, followed by chest discomfort, fever, and headache. Three patients aged 13–18 years, who presented with chest pain and biomarker elevation, were evaluated; all three presented 24–48 h after receiving the second dose of the vaccine. Four patients had no symptoms but elevated cTnT (peak level 15.44–38.68 ng/L; normal level < 14 ng/L). The characteristics of the patients with elevated biomarkers or positive lab assessments are shown in Table 3. All patients were male and had abnormal electrocardiograms, particularly sinus tachycardia. The clinical course was mild in all patients.

### 3.4. Evaluation of Patients Developing Abnormal ECG Post-Vaccination

After vaccination, ECG revealed that of the 301 patients, 247 (82.06%) had normal sinus rhythm, while an abnormal ECG finding was noted in 54 patients (17.94%) (Table 4). The most common abnormal ECG finding was sinus rhythm with sinus arrhythmia (7.31%), followed by sinus tachycardia (6.64%) and sinus bradycardia (1.33%). Of the two patients with abnormal rhythm, one had junctional escape rhythm, and one had ectopic atrial

rhythm. Arrhythmia was observed as premature ventricular contractions in two patients (0.66%), and three (1%) had premature atrial contraction. One case (0.33%) had diffused ST elevation with PR depression.

**Table 3.** Characteristic of patients with elevated biomarker levels or positive lab assessments.

| | Demographic | | | Clinical Presentation | | | | | | | | | | | Echocardiography | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. | Age (y) | Sex | Classification | Peak CRP (mg/L) | Peak ESR (mm/hr) | CK-MB Level (ng/mL) | | | | Troponin-T (pg/mL) | | | | LVEF% | | | | Pericardial Effusion |
| | | | | | | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | |
| 1 | 16 | Male | Myopericarditis | 86.6 | 19 | 1.25 | 109.6 | 2.36 | 1.67 | 3.18 | 593 | 37.2 | 10.9 | 75.3 | 73.7 | 77.2 | 84.7 | Yes |
| 2 | 15 | Male | Pericarditis | 1.3 | 7 | 1.11 | 1.34 | 1.52 | 1.46 | 2.58 | 3.77 | 6.04 | 3.93 | 61.5 | 60.2 | 74.1 | 70.7 | Yes |
| 3 | 17 | Male | Pericarditis | 10.5 | 8 | 1.99 | 1.87 | 1.72 | 2.71 | 4.54 | 8.03 | 7.87 | 6.75 | 78.9 | 77.5 | 61.0 | 67.2 | Yes |
| 4 | 13 | Male | Subclinical myocarditis | 0.3 | - | 1.39 | 1.72 | 2.28 | - | 8.56 | 10.3 | 34.94 | - | 58.6 | 59.2 | 75.4 | - | No |
| 5 | 14 | Male | Subclinical myocarditis | 0.5 | - | 3.00 | 2.06 | 3.06 | - | 3.73 | 28.6 | 38.68 | - | 79.6 | 60.1 | 76.2 | - | No |
| 6 | 13 | Male | Subclinical myocarditis | 0.9 | - | 3.90 | 3.67 | 5.10 | - | 5.35 | 14.87 | 16.81 | - | 64.3 | 76.2 | 78.9 | - | No |
| 7 | 17 | Male | Subclinical myocarditis | 4.3 | - | 2.25 | 2.32 | 2.41 | - | 3.12 | 13.06 | 15.44 | - | 70.8 | 52.4 | 53.8 | - | No |

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CK-MB, creatine kinase-myocardial band; LVEF, left ventricular ejection fraction.

**Table 4.** Electrocardiographic findings after second vaccine dose.

| Rhythm | Number (*n* = 301) |
|---|---|
| Normal sinus rhythm | 247 (82.06%) |
| Sinus rhythm with sinus arrhythmia | 22 (7.31%) |
| Sinus tachycardia | 20 (6.64%) |
| Sinus bradycardia | 4 (1.33%) |
| Premature atrial contraction (PAC) | 3 (1%) |
| Premature ventricular contraction (PVC) | 2 (0.66%) |
| Junctional escape rhythm | 1 (0.33%) |
| Ectopic atrial rhythm | 1 (0.33%) |
| Diffuse ST elevation with PR depression | 1 (0.33%) |

Data are reported as percentage (%). PAC, premature atrial contraction; PVC, premature ventricular contraction.

### 3.5. Evaluation of Patients with Serial Echocardiographic Findings

All participants underwent a follow-up echocardiography examination at baseline, Day 3, Day 7, and Day 14 (optional). There were no significant differences between the echocardiographic findings by study day, as shown in Table 5.

**Table 5.** Comparison between cardiac function on day of baseline (D0), Day 3 after the second vaccine dose (D3), and Day 7 after the second vaccine dose (D7).

| Cardiac Function | Day0 | Day3 | Day7 | *p*-Value D0 vs. D3 | *p*-Value D0 vs. D7 | *p*-Value D3 vs. D7 |
|---|---|---|---|---|---|---|
| IVSD, mean ± SD | 1.18 ± 4.83 | 0.99 ± 1.51 | 0.93 ± 1.32 | 0.508 | 0.383 | 0.596 |
| LVIDd, mean ± SD | 4.43 ± 3.22 | 4.34 ± 3.02 | 4.81 ± 5.02 | 0.735 | 0.209 | 0.168 |
| LVPWd, mean ± SD | 0.96 ± 0.67 | 0.91 ± 0.81 | 1.28 ± 5.16 | 0.431 | 0.299 | 0.234 |
| LVIDs, mean ± SD | 2.64 ± 1.65 | 2.85 ± 2.82 | 2.60 ± 0.5 | 0.250 | 0.730 | 0.128 |

**Table 5.** *Cont.*

| Cardiac Function | Day0 | Day3 | Day7 | *p*-Value D0 vs. D3 | *p*-Value D0 vs. D7 | *p*-Value D3 vs. D7 |
|---|---|---|---|---|---|---|
| LVEF, mean ± SD | 68.68 ± 9.27 | 68.21 ± 9.18 | 68.30 ± 8.56 | 0.490 | 0.585 | 0.878 |
| MV flow E-wave velocity mean ± SD | 99.32 ± 18.77 | 98.98 ± 20.47 | 99.93 ± 21.05 | 0.791 | 0.773 | 0.391 |
| MV flow A-wave velocity mean ± SD | 53.37 ± 16.10 | 52.39 ± 15.39 | 51.23 ± 16.18 | 0.432 | 0.046 | 0.217 |
| MV annulus E-wave velocity, mean ± SD | 2.11 ± 1.28 | 2.03 ± 0.63 | 2.06 ± 1.18 | 0.281 | 0.632 | 0.653 |
| e′, mean ± SD | 0.12 ± 0.05 | 0.13 ± 0.10 | 0.18 ± 0.55 | 0.227 | 0.097 | 0.065 |
| E/e′, mean ± SD | 8.33 ± 2.63 | 8.22 ± 2.03 | 9.29 ± 8.27 | 0.551 | 0.277 | 0.125 |
| a′, mean ± SD | 0.08 ± 0.06 | 0.08 ± 0.04 | 0.16 ± 0.79 | 0.393 | 0.201 | 0.091 |

Data are presented as means ± standard deviations. *p*-values correspond to paired *t*-tests. a′, late (atrial) diastolic mitral annular velocity; e′, early diastolic mitral annular velocity; E/e′, ratio of peak early mitral inflow velocity to early diastolic mitral annular velocity; IVSD, interventricular septal end diastole; LVEF, left ventricular ejection fraction; LVIDS, left ventricular internal diameter end systole; LVIDd, left ventricular internal diameter end diastole; LVPWd, left ventricular posterior wall end diastole; MV, mitral valve.

## 4. Discussion

This prospective cohort study focuses on cardiovascular manifestations after BNT162b2 mRNA vaccination. Immunization against COVID-19 infection using mRNA-based vaccines is a new technology [20]. On 10 May 2021, the US Food and Drug Administration (USFDA) expanded the use of the Pfizer–BioNTech vaccine to include adolescents aged 12–15 years [21]. In the COVID-19 era, the risks of myocarditis after an mRNA vaccine injection, especially in male adolescents, have raised particular concerns. In July 2021, the CDC reported an association between COVID-19 mRNA vaccines and suspected cases of myocarditis and pericarditis. The incidence rate of myocarditis/pericarditis after mRNA COVID-19 vaccine was reported to be as low as 12.6 cases per million second dose mRNA vaccines among those aged 12–39 years [8,15]. In contrast, our study found one case of myopericarditis, four cases of subclinical myocarditis, and two cases of pericarditis among 301 participants, and each case had mild symptoms. The incidence of myocarditis/pericarditis found in our study may be higher than the other studies due to the study protocol, which required determining baseline troponin-T, CK-MB, ECG, and echocardiography before vaccination. Two retrospective studies from Israel [8,9] showed a slightly different incidence compared with CDC data, possibly resulting from different data collection methods and different criteria for diagnosing myocarditis. Montgomery and colleagues reported on 23 male military personnel diagnosed with myocarditis after presenting with acute sudden onset of chest pain within 4 days after mRNA COVID-19 vaccine [22]. Another prospective study reported six males who were hospitalized with suspected myocarditis, all shortly after a second dose of BNT162b2 mRNA COVID-19 vaccine [23].

The potential mechanism of mRNA COVID-19 vaccine-induced myocarditis remains unknown. It has been suggested that excessive innate immune activation by both lipid nanoparticle and RNA components of COVID-19 vaccines can cause myocarditis [24,25]. Endosomal toll-like receptor (TLR) TLR3, TLR7, and TLR8 in immune cells and RIG-I and MDA5 in nonimmune cells act as a natural defense against foreign RNA but can cross-react with in vitro transcribed (IVT) RNA [26]. The activation of these receptors triggers an inflammatory cascade, assembly of inflammasome platform production of type I interferons, and nuclear translocation of NK-kB [24,25,27]. Inflammasomes are large multiproteins that

are responsive to pathogen- and stress-associated cellular insults. Inflammasomes lead to the secretion of the pleiotropic IL-1 family (IL-1β and IL-18), and pyroptosis [28]. In one case report, patients with vaccine-induced myocarditis had increased levels of interleukin 1 (IL-1) receptor antagonist, interleukin 5 (IL-5), and interleukin 16 (IL-16) [5]. Myocarditis associated with COVID-19 mRNA vaccination mainly occurs in male teenagers within 1 week post-vaccination, typically the second dose vaccination, with recovery of cardiac function within 1–5 weeks after hospitalization [8,12]. The mechanism is unknown, but may be related to the mRNA sequence that encodes for the spike protein of SARS-CoV-2, or the immune response following vaccination [18,29]. By contrast, the incidence of COVID-19-associated cardiac injury or myocarditis is much higher, estimated to be 100 times higher than mRNA COVID-19-related myocarditis [30,31]. Moreover, mRNA vaccine-related myocarditis is characterized by overall mild presentation and favorable outcomes. In our study, chest pain was considered an alarming side effect after BNT162b2 mRNA vaccine injection. Although clinical symptoms spontaneously resolved rapidly in all patients, the potential for cardiac fibrosis vaccine-related myocarditis remains unknown. The long-term outcomes of COVID-19 vaccine have not been described, but in our study nearly 100% of patients with symptoms had recovered within 1–2 weeks, concordant with another study [18]. Long-term surveillance with follow-up cardiac imaging, especially cardiac MRI in patients with vaccine-related myocarditis, is required.

In this study, one patient who was admitted to the ICU Department with negative PCR for COVID-19, was diagnosed with myopericarditis after mRNA COVID-19 vaccine, and showed abnormalities in cardiac enzymes (troponin-T, CK-MB), ECG, echocardiography, and cardiac MRI. As our patient remained clinically stable, endomyocardial biopsy was not indicated during hospitalization. He was treated with ibuprofen for 2 weeks without guideline-directed medical therapy for heart failure because his imaging showed normal LVEF. Treatment of vaccine-induced myocarditis includes corticosteroids, NSAIDs, colchicine, and, in severe cases, IVIG [32,33]. Corticosteroids have been proposed for the treatment of vaccine-induced myocarditis [33]. Nonpharmacological strategies to prevent cardiovascular side effects of COVID-19 vaccination include oral and systemic administration of ascorbic acid. An observational study has found that low serum ascorbic acid can increase cardiovascular disease in humans [34]. Ascorbic acid can prevent cardiotoxic events and can reduce the relative risk for cardiovascular events that could reduce inflammation related to cardiovascular events after COVID-19 vaccination [35]. All patients with subclinical myocarditis had elevated troponin-T without CK-MB elevation; troponin-T level was also highly sensitive for post-vaccination screening for myocarditis. Two patients diagnosed with pericarditis had normal troponin-T levels, but generally raised c-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). All seven patients with elevated biomarker levels or positive lab assessments showed normal left ventricular ejection fraction (LVEF), and only three patients had minimal pericardial effusion. Conventional echocardiography may not be the ideal diagnostic tool in suspected vaccine-induced myocarditis because of its mild clinical symptoms; conventional echocardiography appeared normal in these patients. Speckle tracking echocardiography (STE) strain and strain-rate parameters are useful diagnostic measures with high sensitivity for the early detection of subclinical ventricular dysfunction [36], and cardiac MRI may be the best way to confirm a diagnosis of myocarditis in the majority of cases. In this study, the disease course was mild in all of our patients with cardiac symptoms; they were treated with ibuprofen for 2 weeks and cardiac enzymes returned to normal after 1–2 weeks of outpatient treatment. Myocarditis may have more severe clinical manifestations requiring inotropic drug or mechanical support; however, one patient with myopericarditis in our study follow-up with cMRI at 5 months post-vaccination showed complete recovery and no scar. If an adolescent presents with myopericarditis after COVID-19 mRNA vaccination, a booster shot is contraindicated.

This study had some limitations. Due to the national Thai vaccination campaign against the COVID-19 pandemic, the government declared the timing for the first mRNA COVID-19 vaccine dose urgently, so there was limited time for the Ethics Committee (EC)

to process the first dose; however, myocarditis/pericarditis was more common with the second mRNA COVID-19 vaccination dose. Our study included some participants with subclinical myocarditis presenting without symptom other than elevated troponin-T. It was necessary to request parental permission for blood testing on Day 14, which may have limited participation.

Strengths: this is the first prospective study in Thailand during the national campaign of vaccination against the COVID-19 pandemic for adolescents. The strengths of our study include its prospective design employing serial cardiac enzyme, ECG, and echocardiographic measurements at three separate visits (baseline, Day 3, and Day 7). Two cardiologists at different institutions worked together to confirm the diagnoses of myocarditis, myopericarditis, and pericarditis. Another strength of this study is that participants and parents were able to contact the principal investigators directly online or by telephone for consultation and immediate treatment.

## 5. Conclusions

In this observational study, clinically suspected myopericarditis was temporarily associated with the BNT162b2 mRNA COVID-19 vaccine in a small proportion of adolescent patients. Chest pain is an alarming symptom in patients receiving BNT162b2 mRNA COVID-19 vaccination, especially a second dose of BNT162b2. The risk for these symptoms was found to be higher than reported elsewhere. The adverse cardiovascular manifestations observed in this adolescent cohort were both mild and transient.

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# Epidemiology of Acute Myocarditis/Pericarditis in Hong Kong Adolescents Following Comirnaty Vaccination

Gilbert T. Chua,[1,2,a,] Mike Yat Wah Kwan,[3,a] Celine S. L. Chui,[4,5,6] Robert David Smith,[4] Edmund Chi-Lok Cheung,[7] Tian Ma,[6] Miriam T. Y. Leung,[6,7] Sabrina Siu Ling Tsao,[1,2] Elaine Kan,[8] Wing Kei Carol Ng,[8] Victor Chi Man Chan,[9] Shuk Mui Tai,[9] Tak Ching Yu,[9] Kwok Piu Lee,[9] Joshua Sung Chih Wong,[3] Ying Kit Lin,[3] Chi Chiu Shek,[3] Agnes Sze Yin Leung,[10] Chit Kwong Chow,[11] Ka Wah Li,[12] Johnny Ma,[13,14,15,16] Wai Yuk Fung,[13,14,15,16] Daniel Lee,[17] Ming Yen Ng,[18,19] Wilfred Hing Sang Wong,[1] Hing Wai Tsang,[1] Janette Kwok,[20] Daniel Leung,[1] Kin Lai Chung,[21] Chun Bong Chow,[1] Godfrey Chi Fung Chan,[1,2] Wing Hang Leung,[1,2] Kelvin Kai Wang To,[22,] Kwok Yung Yuen,[22] Yu Lung Lau,[1,2] Ian Chi Kei Wong,[6,7,23] and Patrick Ip[1]

[1]Department of Pediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China; [2]Department of Paediatrics, Hong Kong Children's Hospital, Hong Kong SAR, China; [3]Department of Pediatrics and Adolescent Medicine, Princess Margaret Hospital, Hong Kong SAR, China; [4]School of Nursing, The University of Hong Kong, Hong Kong SAR, China; [5]School of Public Health, The University of Hong Kong, Hong Kong SAR, China; [6]Laboratory of Data Discovery for Health (D24H), Hong Kong Science and Technology Park, Hong Kong SAR, China; [7]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong SAR, China; [8]Department of Radiology, Hong Kong Children's Hospital, Hong Kong SAR, China; [9]Department of Paediatrics and Adolescent Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong SAR, China; [10]Department of Pediatrics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong SAR, China; [11]Department of Pediatrics and Adolescent Medicine, United Christian Hospital, Hong Kong SAR, China; [12]Department of Pediatrics and Adolescent Medicine, Tuen Mun Hospital, Hong Kong SAR, China; [13]Department of Radiology, Caritas Medical Centre, Hong Kong SAR, China; [14]Department of Radiology, North Landau Hospital, Hong Kong SAR, China; [15]Department of Radiology, Princess Margaret Hospital, Hong Kong SAR, China; [16]Department of Radiology, Yan Chai Hospital, Hong Kong SAR, China; [17]Department of Radiology, Pamela Youde Nethersole Eastern Hospital, Hong Kong SAR, China; [18]Department of Diagnostic Radiology, The University of Hong Kong, China; [19]Department of Medical Imaging, The University of Hong Kong-Shenzhen Hospital, China; [20]Division of Transplantation and Immunogenetics, Department of Pathology, Queen Mary Hospital, Hong Kong SAR, China; [21]Quality and Safety Division, Hospital Authority Head office, Hong Kong SAR, China; [22]Department of Microbiology, Carol Yu Centre for Infection, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China; and [23]Research Department of Practice and Policy, UCL School of Pharmacy, University College, London, United Kingdom

***Background.*** Age-specific incidence of acute myocarditis/pericarditis in adolescents following Comirnaty vaccination in Asia is lacking. This study aimed to study the clinical characteristics and incidence of acute myocarditis/pericarditis among Hong Kong adolescents following Comirnaty vaccination.

***Methods.*** This is a population cohort study in Hong Kong that monitored adverse events following immunization through a pharmacovigilance system for coronavirus disease 2019 (COVID-19) vaccines. All adolescents aged between 12 and 17 years following Comirnaty vaccination were monitored under the COVID-19 vaccine adverse event response and evaluation program. The clinical characteristics and overall incidence of acute myocarditis/pericarditis in adolescents following Comirnaty vaccination were analyzed.

***Results.*** Between 14 June 2021 and 4 September 2021, 33 Chinese adolescents who developed acute myocarditis/pericarditis following Comirnaty vaccination were identified. In total, 29 (87.88%) were male and 4 (12.12%) were female, with a median age of 15.25 years. And 27 (81.82%) and 6 (18.18%) cases developed acute myocarditis/pericarditis after receiving the second and first dose, respectively. All cases are mild and required only conservative management. The overall incidence of acute myocarditis/pericarditis was 18.52 (95% confidence interval [CI], 11.67–29.01) per 100 000 persons vaccinated. The incidence after the first and second doses were 3.37 (95% CI, 1.12–9.51) and 21.22 (95% CI, 13.78–32.28 per 100 000 persons vaccinated, respectively. Among male adolescents, the incidence after the first and second doses were 5.57 (95% CI, 2.38–12.53) and 37.32 (95% CI, 26.98–51.25) per 100 000 persons vaccinated.

***Conclusions.*** There is a significant increase in the risk of acute myocarditis/pericarditis following Comirnaty vaccination among Chinese male adolescents, especially after the second dose.

**Keywords.** myocarditis; pericarditis; adolescents; Comirnaty; Hong Kong.

The coronavirus disease 2019 (COVID-19) infection in children is generally mild, but serious complications, such as pediatric multisystem inflammatory syndrome—temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (PIMS-TS), can occur [1]. Prolonged social distancing policies have also led to significant psychosocial impacts on children and their families in the community [2]. Enormous efforts have been made to control the spread of the virus through universal vaccination to achieve herd immunity to return us to a semblance of normality.

Currently, the vaccination program of the Hong Kong Government has authorized 2 COVID-19 vaccines: the CoronaVac from Sinovac Biotech (Hong Kong) Limited and Comirnaty vaccine (BNT162b2) from Fosun-BioNTech. On 14 June 2021, the government of the Hong Kong Special Administrative Region (HKSAR) commenced vaccination of the Comirnaty vaccine (BNT162b2) from Fosun-BioNTech

to adolescents by lowering of the age limit from 16 to 12 years after reviewing the available evidence by the advisory panel on COVID-19 Vaccines of the Food and Health Bureau, HKSAR Government [3]. The drug office of the Department of Health (DH), the drug regulatory authority in Hong Kong, has implemented a pharmacovigilance system for COVID-19 vaccines that monitors reports of adverse events following immunization (AEFI). The COVID-19 vaccine Adverse event Response and Evaluation (CARE) program was set up, an active surveillance system, to evaluate AEFI data from the general population using electronic medical records from Hospital Authority and vaccination records from the DH. The CARE program actively identifies AEFI and conduct epidemiological study to evaluate the association between vaccinations and subsequent adverse event [4, 5].

The Comirnaty is a messenger RNA (mRNA) vaccine that is highly effective in preventing hospitalizations and deaths due to COVID-19 [6]. Although Comirnaty has a favorable safety profile, various regulatory agencies have advocated continuous monitoring of its safety, as rare and long-term adverse reactions might not have been detected in the clinical trials and early post-marketing reports [7]. Recently, there have been emerging case reports of acute myocarditis following mRNA COVID-19 vaccination in healthy young adolescent and adult males [8–10]. The United Kingdom has only approved offering 1 dose of the Pfizer-BioNTech vaccine to healthy adolescents aged 12–15 years old so far, instead of giving the recommended 2 doses [11]. Yet an in-depth population-based investigation of the age-specific incidence of acute myocarditis/pericarditis following mRNA COVID-19 vaccination in Asian adolescents is lacking. This study aims to report the clinical characteristics and estimate the incidence of acute myocarditis following vaccination with Comirnaty in adolescents in Hong Kong.

## METHODS

This was a population cohort study aimed at identifying all suspected cases of acute myocarditis in adolescents aged between 12 and 17 years who received the Comirnaty vaccine between 14 June 2021 and 4 September 2021. All individuals receiving the Comirnaty vaccine have also consented to their vaccination records being linked to their corresponding comprehensive electronic health records held by the Hospital Authority (HA), the major publicly funded healthcare provider, through the CARE program [4]. All suspected cases of acute myocarditis/pericarditis that occur within 14 days after receiving either the first or the second dose of the Comirnaty vaccine and admitted to one of the HA hospitals are reported to the Advanced Incident Reporting System (AIRS) on admission, a system for HA to report adverse drug events and AEFI to DH.

Suspected cases of acute myocarditis/pericarditis who received Comirnaty vaccines during the study period were investigated according to the Hong Kong Pediatric Investigation Protocol for Comirnaty-related Myocarditis/Pericarditis (Supplementary file 1), which was implemented in all HA hospitals. Demographics including date of birth, sex, ethnicity, date of receiving the first and the second dose of COVID-19 vaccines, symptoms, date of onset, and past medical histories were reviewed. Microbiological investigations including nasopharyngeal swab (NPS) for SARS-CoV-2 and common respiratory viruses including influenza A/B/C, parainfluenza virus 1/2/3/4, adenovirus, human metapneumovirus, and respiratory syncytial virus, and throat and rectal swabs for enteroviruses were tested. SARS-CoV-2 anti-receptor binding domain (RBD) and anti-nucleocapsid protein (NP) antibodies were tested to differentiate whether the patients had a history of COVID-19 infection. Cardiac enzymes, including high-sensitivity troponin I (hsTnI), high-sensitivity troponin T (hsTnT or TnT), electrocardiogram (ECG), and echocardiogram were serially monitored. ECGs were interpreted by 1 single investigator (S. S. T.). Echocardiograms were performed and interpreted by the cardiologists of each admitting hospital. Cardiac magnetic resonance imaging (cMRI) was performed within two weeks of symptoms onset either at the admission hospital, or referred to the Hong Kong Children's Hospital if no slots were immediately available. The cMRI images were interpreted by the radiologists of each magnetic resonance imaging (MRI) unit. The study team followed the myocarditis and pericarditis case definitions created by the Cardiovascular Injury-Coalition for Epidemic Preparedness Innovations (CEPI) and the Brighton Working Group [12].

### Estimation of Incidence and Statistical Analysis

Vaccination records within the study period were extracted from the DH in Hong Kong since the commencement of mass COVID-19 vaccinations in adolescents aged 12–17 years on 14 June 2021 to 4 September 2021. The cutoff date for follow-up time was 18 September 2021, allowing for all participants to have a 14-day follow-up period. De-identified electronic health records were retrieved from the HA Clinical Data Analysis and Reporting System (CDARS), which has been successfully used in a previous COVID-19 vaccine-related pharmacovigilance study [4]. Subjects with a history of primary myocarditis/pericarditis prior to the study period were excluded. Cases of acute myocarditis/pericarditis following Comirnaty vaccination were identified if they occurred within 14 days of either the first or the second vaccine dose. We estimated the background rate of acute myocarditis/pericarditis, cases of the first primary diagnosis were extracted from CDARS from 2011 to 2020 using data available from 14 June to 4 September of each year. For each year, those with a history of acute myocarditis/pericarditis in the prior year to the study period were censored.

Separated cases related to the first dose or to the second dose were also calculated. Acute myocarditis/pericarditis related to

the first dose was defined as the first cases within 14 days of the first dose. Acute myocarditis/pericarditis related to the second dose was defined as the first cases within 14 days of the second dose. The 14 days was the upper end of the reporting of myocarditis/pericarditis cases following vaccination according to the DH and HA reporting policies. The incidence of clinically confirmed myocarditis/pericarditis per 100 000 doses administered as well as number of cases per 100 000 doses for first dose and second dose were estimated. We calculated 95% confidence intervals (CI) for all incidences calculated using Poisson distribution. The incidence rate of acute myocarditis/pericarditis associated with the Comirnaty vaccine was compared with the background incidence rate of acute myocarditis/pericarditis in 2020 using 100 000 doses per 14-days. Sensitivity analyses were conducted using (1) the background incidence rate in 2018 and 2019 and the average background incidence rate from 2011 to 2020 using 100 000 doses per 14 days and (2) changed the incidence using doses per 28 days. Subgroup analysis was conducted by sex. Some comparisons to background years were not possible as there were zero cases of myocarditis/pericarditis recorded in background years. Median and interquartile ranges (IQR) were used to describe skewed data. All statistical tests were 2-sided, and *P*-values at a level of 5% were considered statistically significant. Statistical analyses were conducted using R version 4.0.3 (www.R-project.org). For quality assurance, 2 investigators (E. C. C. and R. D. S.) independently conducted the statistical analyses.

### Ethical Approval

This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW21-149 and UW21-138) and the Department of Health Ethics Committee (LM21/2021).

## RESULTS

Between 14 June and 4 September 2021, a total of 33 cases of myocarditis/pericarditis within 14 days following vaccination with Comirnaty were identified. Twenty-five (75.76%) were definite, 7 (21.21%) were probable, and 1 (3.03%) were possible cases (Table 1). The patients were all Chinese adolescents with no history of cardiac diseases; 29 (87.88%) were male and 4 (12.12%) were female, with a median age of 15.25 years. In total, 27 (81.82%) and 6 (18.18%) cases developed acute myocarditis/pericarditis after receiving the second and first dose, respectively. These patients developed myocarditis/pericarditis at a median of 2 days after receiving the last dose of the vaccine. All of them presented with chest pain. Three cases (9.09%) had normal troponin levels, 2 of them were cases of definite pericarditis and 1 had possible myocarditis. Six (18.18%) had normal ECGs, 25 (75.76%) had normal echocardiograms, and 7 (21.88%) had normal cMRI. None had

significant arrhythmias. All patients had no identifiable infections. They also had no current and past history of COVID-19 infection, as evidenced by a negative SARS-CoV-2 PCR on admission and the absent of anti-SARS-CoV-2 NP antibodies in their serum. All patients had mild diseases requiring no treatment or symptomatic relief by nonsteroidal anti-inflammatory drugs (NSAIDs). They spontaneously recovered without the need of systemic steroids, intravenous immunoglobulins, or inotropic or circulatory support.

There have been 305 406 doses of Comirnaty vaccine administered to 178 163 individuals aged 12–17 years (88 357 [49.59%] are female) since the commencement of the vaccination program on 14 June 2021 until 4 September 2021. This represented 51.84% of the population between 12 and 17 years (178 163/343 700) in Hong Kong in mid-2021 [13]. The overall incidence for acute myocarditis/pericarditis was 18.52 (95% CI, 11.67–29.09) per 100 000 persons. The incidence after the first and second doses were 3.37 (95% CI, 1.12–9.51) and 21.22 (95% CI, 13.78–32.28) per 100 000 persons vaccinated, respectively (Table 2). Incidence was higher among male adolescents compared to females (Table 2). Incidence rates compared with previous years' background rates are shown in Table 2 and Supplementary Tables 1–3. Compared to the background incidence rate of acute myocarditis/pericarditis in 2020 there were significantly higher incidence rate differences in those vaccinated (Table 2). Sensitivity analyses using the background incidence rate in 2018, 2019, and 2020 and the average background incidence rate from 2011 to 2020 using per 100 000 per 28-days also demonstrated significantly higher incidence rate differences in those vaccinated which was consistent with the main results (Supplementary Tables 4–8).

Among males after their first dose, there was a significantly higher incidence rate difference compared the background rate in 2020. After the second dose there was significantly higher incidence rate difference between the background rate in 2020 and all participants and males (Table 3).

## DISCUSSION

To our best knowledge, this is the first study in adolescents using data from the territory-wide post-COVID-19 vaccination monitoring system to analyze the incidence of acute myocarditis/pericarditis associated with the Comirnaty vaccine for adolescents in Asia.

Our analysis revealed that the overall incidence of acute myocarditis/pericarditis in adolescent following the Comirnaty vaccination was 18.52 per 100 000 persons vaccinated. Majority cases involved healthy adolescent males after receiving the second dose. No other infective causes including SARS-CoV-2 infection were identified. Conservative management with NSAIDs was sufficient. This higher

**Table 1. Clinical Characteristics of Adolescents With Myocarditis/Pericarditis Following Comirnaty Vaccination in Hong Kong**

| No. | Sex/Age at Presentation (years) | Present After First or Second Dose | No. of Days After Receiving the Last Dose | Symptoms | Peak Troponin Levels (hsTnT/hsTnI/TnT) (ng/L)[b] | Most Significant ECG Changes | ECHO | MRI Findings | Final Diagnosis (Level of Certainty[a]) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M/15.66 | Second | 2 | Chest pain, headache | TnT 793 hsTnI 2506 (elevated) | STE in II, III, aVF, V3-V5 | Normal | Patchy edema; diffuse EGE; patchy pericardial and subepicardial LGE; normal ECV | Perimyocarditis (Definite) |
| 2 | M/14.52 | Second | 1 | Chest pain, fever | TnT 646 hsTnI 6342 (elevated) | TWI and biphasic T waves in III, aVF; V4-V6 | Normal | Borderline LV function; elevated T1 and T2 mapping values and ECV; presence of LGE | Myocarditis (Definite) |
| 3 | M/13.53 | Second | 2 | Dizziness, SOB, chest pain | TnT 1749 (elevated) | STE in V2-V6TWI in aVL; biphasic Ts in V3-V4 | Normal | Elevated T1 and T2 mapping values and ECV; pericardium and subepicardial muscles LGE and T2 hyperintensity | Perimyocarditis (Definite) |
| 4 | M/13.05 | First | 2 | Chest pain | TnT 302 (elevated) | STE in V3-V6; TWI in III; STD in aVR | Normal | Elevated T1 and T2 mapping values and ECV; pericardial LGE extending to subepicardial region | Perimyocarditis (Definite) |
| 5 | M/14.34 | Second | 1 | Chest pain | TnT 993 (elevated) | STE in V3-V5; TWI in I, aVL; biphasic T waves in V3-V6 | Normal | Borderline LV function; subepicardial LGE; elevated T1 and T2 mapping values and ECV; hyperintense pericardium | Perimyocarditis (Definite) |
| 6 | M/16.99 | Second | 3 | Chest pain | TnT 948 (elevated) | STE in V2-V6 | Mildly impaired LV global longitudinal strain | Borderline LV function, small pericardial effusion; elevated ECV, T1 and T2 mapping values; patchy LGE | Perimyocarditis (Definite) |
| 7 | M/15.22 | Second | 2 | Chest pain | hsTnI 11415 (elevated) | Normal | Normal | Elevated T1 and T2 mapping values; presence of patchy EGE; normal ECV; subepicardial LGE | Myocarditis (Definite) |
| 8 | M/15.32 | Second | 2 | Chest pain, fever | hsTnI 16806 (elevated) | STD and TWI in V1-2; STE in lead II, III, aVF; ST/T wave abnormality in II, III, aVF, V4-V6 | Borderline LV function (LVFS 28%), minimal pericardial effusion | Mild increase STIR signal; faint patchy LGE; trace pericardial effusion | Perimyocarditis (Definite) |
| 9 | M/17.14 | First | 1 | Chest pain | hsTnI 19110 (elevated) | STE in II, III, aVF, V4-V6 | Tiny rim of pericardial effusion | Elevated T1 and T2 mapping values and ECV; no definite EGE; LGE present; patchy pericardial enhancement | Perimyocarditis (Definite) |
| 10 | F/14.07 | Second | 3 | Chest discomfort, transient SOB | hsTnI 54.9 (elevated) | STE in V4-V5 | Normal | Elevated T1 and T2 mapping values and ECV; LGE and pericardial enhancement | Perimyocarditis (Definite) |
| 11 | M/13.75 | Second | 2 | Chest pain, palpitation, fever | hsTnI 6254 (elevated) | Sinus tach; STE in II, III, aVF, V3-V5 | Normal | Elevated T1 and T2 mapping values and ECV; presence of LGE | Myocarditis (Definite) |
| 12 | M/12.74 | Second | 1 | Chest pain, palpitations, dizziness | hsTnI 14766 (elevated) | STD in aVR and V1; STE I-III; aVF; V4-V6 | Thin rim of pericardial effusion, hyperechoic pericardium | Elevated T1 mapping value; presence of myocardial edema with increased T2W signal | Perimyocarditis (Definite) |
| 13 | F/12.97 | Second | 1 | Chest pain, fever, headache, palpitations, subjective SOB | hsTnI 2309 (elevated) | Normal | Normal | Elevated T1 and T2 mapping values and ECV; pericardial and subepicardial LGE; small pericardial effusion | Perimyocarditis (Definite) |
| 14 | M/17.85 | Second | 3 | Chest pain | hsTnI 30267 (elevated) | STE in I, II, aVF, V4-V6, STD in aVR, V1-V2; TWI in III; biphasic Ts in V3-V5 | Borderline contractility | Elevated T1 and T2 mapping values and ECV; subepicardial and mid-wall LGE; small pericardial effusion | Perimyocarditis (Definite) |

**Table 1. Continued**

| No. | Sex/Age at Presentation (years) | Present After First or Second Dose | No. of Days After Receiving the Last Dose | Symptoms | Peak Troponin Levels(hsTnT/hsTnI/TnT) (ng/L)[b] | Most Significant ECG Changes | ECHO | MRI Findings | Final Diagnosis (Level of Certainty)[a] |
|---|---|---|---|---|---|---|---|---|---|
| 15 | M/14.99 | Second | 1 | Fever, chest pain, palpitation, SOB, dizziness | TnT 323 (elevated) | STE in V3-5TWI in aVR and V1 | Normal | T2W hyperintensity within myocardium; regional LGE; 5mm pericardial effusion | Perimyocarditis (Definite) |
| 16 | M/16.88 | Second | 4 | Chest pain, SOB | hsTnT < 14 (normal) | STE in V2 and V4 | Increased echogenicity over LV free wall | Not done | Pericarditis (Definite) |
| 17 | M/17.33 | Second | 2 | Chest pain, fever, palpitation | hsTnI 767 (elevated) | STE in II, III, aVF, V3–V6 | Normal | T2W hyperintense myocardial edema at mid and apex of LV | Myocarditis (Definite) |
| 18 | M/14.25 | First | 3 | Chest pain, fever | hsTnI 184 (elevated) | STD in II, III, aVF | Normal | T2W hyperintense myocardial edema at basal lateral and basal septal segments of LV | Myocarditis (Definite) |
| 19 | M/15.95 | Second | 2 | Chest discomfort, palpitation | hsTnI 3561 (elevated) | STE in II, aVF; V4–V6 | Normal | T2W hyperintense myocardial edema with LGE at apical lateral segment and subepicardial region | Myocarditis (Definite) |
| 20 | M/14.17 | Second | 2 | Chest pain | TnT 1058 (elevated) | STE in V4–V6; TWI in III, aVF | Normal | Mild T2W hyperintense signals and increased T2 mapping value at inferolateral LV wall | Myocarditis (Definite) |
| 21 | M/15.70 | Second | 2 | Chest pain | hsTnI 263 (elevated) | STE II, III, aVF; V4–V6 | Normal | Mild subepicardial basal to mid-ventricular lateral wall LGE and elevated T1 mapping value | Myocarditis (Definite) |
| 22 | M/15.65 | Second | 1 | Chest pain, palpitations | hsTnI 2210 TnT 283 (elevated) | STE V2–V6 | Normal | Generalized myocardial hyperintensity in TIRM sequence; presence of hyperemia; subepicardial LGE; small pericardial effusion | Perimyocarditis (Definite) |
| 23 | F/16.89 | First | 2 | Palpitation, near syncope, nausea, vomiting | hsTnT 30 (elevated) | Normal | Normal | LV myocardium diffuse increased T2 signal; patchy early Gd enhancement | Myocarditis (Definite) |
| 24 | M/16.88 | Second | 2 | Chest pain, headache, dizziness | TnT 669 (elevated) | Normal | Borderline LV function(LVFS 29.1%) | Normal | Myocarditis (Definite) |
| 25 | M/14.78 | Second | 2 | Chest pain, palpitation | hsTnT < 14 (normal) | STE in I,II, V2–V6, and STD in aVR | Prominent pericardial echogenicity | Normal | Pericarditis (Definite) |
| 26 | M/14.18 | First | 2 | Chest pain | hsTnI 513 (elevated) | Normal | Normal | Equivocal myocardial edema due to motion artefacts | Myocarditis (Probable) |
| 27 | F/15.25 | Second | 6 | Chest pain | hsTnI 77 (elevated) | STE V2–V3; biphasic Ts in V3 | Normal | Normal | Myocarditis (Probable) |
| 28 | M/14.31 | Second | 14 | Chest discomfort, transient SOB, headache, dizziness | hsTnI 201 (elevated) | TWI and ST depression in II, III, aVF; biphasic Ts in V3–V5 | Normal | Normal | Myocarditis (Probable) |
| 29 | M/17.87 | First | 2 | Chest pain | hsTnI 29.2 (elevated) | STE in II, V3–V6 | Normal | Normal | Myocarditis (Probable) |
| 30 | M/17.64 | Second | 2 | Chest pain, fever, headache | hsTnI 4874 (elevated) | STE in V2–V6, TWI in aVF/III; biphasic Ts in II, aVF, V4–V6 | Normal | Normal | Myocarditis (Probable) |

**Table 1. Continued**

| No. | Sex/Age at Presentation (years) | Present After First or Second Dose | No. of Days After Receiving the Last Dose | Symptoms | Peak Troponin Levels(hsTnT/ hsTnI/TnT) (ng/L)[b] | Most Significant ECG Changes | ECHO | MRI Findings | Final Diagnosis (Level of Certainty[a]) |
|---|---|---|---|---|---|---|---|---|---|
| 31 | M/12.85 | Second | 2 | Chest pain, vomiting, SOB | hsTnT 39 | Sinus tachycardia; STE in II, III, aVF; V2–V6 | Normal | Global hyperintensity in myocardium in T2W images with hyperintensity in early post-Gd images but no LGE. Suspicious of myocarditis | Myocarditis (Probable) |
| 32 | M/15.79 | Second | 10 | Chest pain, dizziness, near syncope | hsTnT 25 (elevated) | Normal | Normal | Normal | Myocarditis (Probable) |
| 33 | M/16.76 | Second | 2 | Fever, chest discomfort, palpitation, transient SOB | hsTnT < 14 (normal) | STE in V2–V6 | Normal | Normal | Myocarditis (Possible—elevated CRP) |
| 34[c] | M/15.07 | Second | 25 | Chest pain | TnT 269 hsTnI 3850 | STE in V2–V6 | Mild pericardial and LV free wall echogenicity | Not done | Perimyocarditis (Definite) |
| 35[c] | F/12.78 | Second | 26 | Vomiting, palpitation, reduced exercise tolerance | hsTnI 566 | STE in II, V2–V5; STD in aVR; TWI in aVL; Q waves in I and aVL | Hyperechoic pericardium | Elevated T1 mapping values; subepicardial LGE | Perimyocarditis (Definite) |

Abbreviations: CRP, C reactive protein; ECG, electrocardiogram; ECHO, echocardiogram; ECV, extracellular volume; EGE, early gadolinium enhancement; Gd, gadolinium; hsTnI, high-sensitivity troponin I; hsTnT, high-sensitivity troponin T; LGE, late gadolinium enhancement; LV, left ventricle; LVFS, left ventricle fractional shortening; MRI, magnetic resonance imaging; SOB, shortness of breath; STD, ST depression; STE, ST elevation; STIR, short tau inversion recovery; T2W, T2-weighted; TWI, T wave inversion; TnT, troponin T.

[a]Brighton Collaboration Myocarditis Case Definition Level of Certainty (LOC) Classification.

[b]Elevated troponin level based on reference values provided by each laboratory. Subjects with two different troponin measures were because of transferal to another hospital.

[c]Cases 34 and 35 presented > 14 days after receiving the second doses, therefore they were only included in the sensitivity analyses (Supplementary Tables 4–8).

**Table 2.** Incidence Rate Differences of Myocarditis/Pericarditis Cases Following Comirnaty Vaccination Stratified by Sex and Compared to Background Rate in 2020

| | Incidence Rate (per 100 000 person-14 days, 95% CI) | Background Incidence Rate in 2020[a] (per 100 000 person-14 days, 95% CI) | Incidence Rate Difference (per 100 000 person-14 days, 95% CI) |
|---|---|---|---|
| Comirnaty | | | |
| Total | 18.52 (11.67–29.01) | 0.11 (.01–20.36) | **18.41 (9.95–26.87)** |
| Male | 32.29 (22.78–45.4) | 0.21 (.01–10.34) | **32.08 (20.91–43.25)** |
| Female | 4.53 (1.76–11.11) | 0 | - |

Values in bold represent a statistically significant difference (*P* < .05).

Abbreviation: CI, confidence interval.

[a]The background incidence rates were calculated using the reporting period (14 June to 4 September) in 2020 and truncated to incidence rate per 14 days.

incidence of myocarditis/pericarditis following Comirnaty vaccination than other jurisdictions is likely related to the heightened vigilance of healthcare professionals and the public [14], as well as the highly efficient CARE program for the monitoring and reporting of AEFI across Hong Kong [10]. Our pharmacovigilance system was able to capture mild cases of acute myocarditis/pericarditis and reveal the real-world incidence of acute myocarditis/pericarditis following the Comirnaty vaccination. Because the Pfizer-BioNTech vaccine was approved for large-scale immunization in many countries, there has been a higher observed risk of acute myocarditis/pericarditis among younger males receiving this vaccine [15]. The first reports in Israel were of 5 young males who developed mild myocarditis following vaccination with the BioNTech mRNA COVID-19 vaccine [16]. Subsequently, 23 US military males reported developing myocarditis after administering more than 2.8 million doses of either the Moderna or BioNTech mRNA COVID-19 vaccines to military personnel [9]. In children, so far, only 1 case series reported myocarditis following vaccinations with mRNA COVID-19 vaccines. These 7 cases were males aged 14–19 years who presented with transient mild symptoms, elevated troponin, and MRI changes suggestive of acute myocarditis or perimyocarditis. They were treated with NSAIDs, steroids, or intravenous immunoglobulin [8]. So far, all adults

and adolescents with myocarditis/pericarditis following COVID-19 vaccinations, including those reported in the current study, have been mild cases [17]. However, the pathophysiology of acute myocarditis/pericarditis following the mRNA COVID-19 vaccine is still unclear, and the observation that only mRNA-based COVID-19 vaccines are associated with acute myocarditis remains unexplained. The causal association between mRNA vaccine and myopericarditis has recently been suggested in a mouse model. Higher systemic levels of mRNA lipid nanoparticles due to inadvertent intravenous injection or rapid return from the lymphatic circulation was proposed to increase this risk [18]. Further studies to delineate the pathophysiology of acute myocarditis/pericarditis associated with mRNA-based COVID-19 vaccines is urgently needed.

The US Center for Disease Control and Prevention (CDC) reported that the expected rates of myocarditis/pericarditis following the Comirnaty vaccination would be the highest among males aged between 12 and 29 years old, estimating 40.6 per million second doses administered [10]. The incidence rate of myocarditis/pericarditis following the Comirnaty vaccination in Hong Kong was much higher than those reported from the United States [10, 19]. However, it is important to note that the risk of myocardial injury in healthy young individuals including athletes following

**Table 3.** Incidence Rate Differences of Myocarditis/Pericarditis Cases Following the First and Second Doses of Comirnaty Vaccination Stratified by Sex and Compared to Background Rate in 2020

| | Incidence Rate (per 100,000 person-14 days, 95% CI) | Background Incidence Rate in 2020[a] (per 100 000 person-14 days, 95% CI) | Incidence Rate Difference (per 100 000 person-14 days, 95% CI) |
|---|---|---|---|
| First dose of Comirnaty | | | |
| Total | 3.37 (1.12–9.51) | 0.11 (.01–20.36) | 3.26 (−0.40 to 6.92) |
| Male | 5.57 (2.38–12.53) | 0.21 (.01—10.34) | **5.36 (0.65–10.07)** |
| Females | 1.13 (0.16–6.58) | 0 | - |
| Second dose of Comirnaty | | | |
| Total | 21.22 (13.78–32.28) | 0.11 (.01–20.36) | **21.11 (12.06–30.16)** |
| Male | 37.32 (26.98–51.25) | 0.21 (.01–10.34) | **37.11 (25.10–49.12)** |
| Female | 4.77 (1.90–11.44) | 0 | - |

Values in bold represent a statistically significant difference (*P* < .05).

Abbreviation: CI, confidence interval.

[a]The background incidence rates were calculated using the reporting period (14 June to 4 September) in 2020 and truncated to incidence rate per 14 days.

COVID-19 infection is also considerably high [20], ranging from asymptomatic cases with abnormal cMRI only to fulminant myocarditis due to COVID-19 [21, 22]. Preliminary data in Israel demonstrated a 51% effectiveness after receiving 1 dose Pfizer-BioNTech vaccine among older adults [23]. As there have been essentially no local transmission of SARS-CoV-2 in Hong Kong since May 2021 [24], balancing the risk of acute myocarditis/pericarditis after receiving the second dose and the benefit of vaccination to protect complications related to COVID-19 infection, the Scientific Committee on Vaccine Preventable Diseases and the Scientific Committee on Emerging and Zoonotic Diseases under the Centre for Health Protection of the Department of Health of Hong Kong recommended adolescents between 12 and 17 years to receive 1 dose of the Comirnaty vaccine, instead of 2 doses, on 15 September 2021 [25]. Although our study provided the most comprehensive epidemiology of myocarditis/pericarditis following Comirnaty vaccination before the policy change, ongoing observations on the incidence of myocarditis/pericarditis following the Comirnaty vaccination with 1-dose Comirnaty vaccination as well as the rate of COVID-19 infections among adolescents in Hong Kong shall be conducted to provide real-world evidence on the risk and benefit of the policy change.

This study has several strengths and limitations. All subjects presented to the accident and emergency department or in the outpatient clinics in the public system received comprehensive reviews and investigations to rule out the possibility of myocarditis/pericarditis because of viral infection, and cMRI to confirm subtle inflammation of the myocardium. However, asymptomatic subjects and subjects with transient and subtle symptoms of acute myocarditis/pericarditis, such as tachycardia and mild chest discomfort, might not seek medical consultation or have sought medical consultation in the private sector which were not reported. Some patients had negative MRI results because not all MRI suites in Hong Kong's public hospitals have the capability for T1 and T2 mapping to calculate the extracellular volume, leading to lower sensitivities and unable to meet the 2018 Lake Louise Criteria for the diagnosis of myocarditis. Furthermore, the incidence of acute myocarditis/pericarditis following the COVID-19 vaccination remained to be high, possibly attributed to increased awareness of possible acute myocarditis/pericarditis following vaccination with COVID-19 vaccines compared with other jurisdictions, as well as to the CARE program to capture AEFI. The high incidence of acute myocarditis/pericarditis following Comirnaty vaccination among adolescents presented in this study is representable as the HA receives majority of emergency admissions in Hong Kong [4]. Finally, different criteria were likely used by clinicians in generating a diagnostic code among the nonvaccinated individuals for the calculation of the background myocarditis/pericarditis incidence as it was in a nonresearch setting.

Nevertheless, we have included myocarditis and pericarditis of all causes, including idiopathic cases, for the calculation of the background incidence.

## Conclusion

Chinese adolescent males have a higher risk of acute myocarditis/pericarditis following vaccination with Comirnaty, especially after the second dose. Medical professionals and recipients of the Comirnaty vaccine should be vigilant regarding the symptoms of acute myocarditis/pericarditis. Observations on the incidence of myocarditis/pericarditis following the Comirnaty vaccination after changing to 1-dose vaccination as well as the rate of COVID-19 infections among adolescents shall be conducted.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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# Outcomes at least 90 days since onset of myocarditis after mRNA COVID-19 vaccination in adolescents and young adults in the USA: a follow-up surveillance study

*Ian Kracalik, Matthew E Oster, Karen R Broder, Margaret M Cortese, Maleeka Glover, Karen Shields, C Buddy Creech, Brittney Romanson, Shannon Novosad, Jonathan Soslow, Emmanuel B Walter, Paige Marquez, Jeffrey M Dendy, Jared Woo, Amy L Valderrama, Alejandra Ramirez-Cardenas, Agape Assefa, M Jay Campbell, John R Su, Shelley S Magill, David K Shay, Tom T Shimabukuro, Sridhar V Basavaraju, for the Myocarditis Outcomes After mRNA COVID-19 Vaccination Investigators and the CDC COVID-19 Response Team*

## Summary

**Background** Data on medium-term outcomes in indivduals with myocarditis after mRNA COVID-19 vaccination are scarce. We aimed to assess clinical outcomes and quality of life at least 90 days since onset of myocarditis after mRNA COVID-19 vaccination in adolescents and young adults.

**Methods** In this follow-up surveillance study, we conducted surveys in US individuals aged 12–29 years with myocarditis after mRNA COVID-19 vaccination, for whom a report had been filed to the Vaccine Adverse Event Reporting System between Jan 12 and Nov 5, 2021. A two-component survey was administered, one component to patients (or parents or guardians) and one component to health-care providers, to assess patient outcomes at least 90 days since myocarditis onset. Data collected were recovery status, cardiac testing, and functional status, and EuroQol health-related quality-of-life measures (dichotomised as no problems or any problems), and a weighted quality-of-life measure, ranging from 0 to 1 (full health). The EuroQol results were compared with published results in US populations (aged 18–24 years) from before and early on in the COVID-19 pandemic.

**Findings** Between Aug 24, 2021, and Jan 12, 2022, we collected data for 519 (62%) of 836 eligible patients who were at least 90 days post-myocarditis onset: 126 patients via patient survey only, 162 patients via health-care provider survey only, and 231 patients via both surveys. Median patient age was 17 years (IQR 15–22); 457 (88%) patients were male and 61 (12%) were female. 320 (81%) of 393 patients with a health-care provider assessment were considered recovered from myocarditis by their health-care provider, although at the last health-care provider follow-up, 104 (26%) of 393 patients were prescribed daily medication related to myocarditis. Of 249 individuals who completed the quality-of-life portion of the patient survey, four (2%) reported problems with self-care, 13 (5%) with mobility, 49 (20%) with performing usual activities, 74 (30%) with pain, and 114 (46%) with depression. Mean weighted quality-of-life measure (0·91 [SD 0·13]) was similar to a pre-pandemic US population value (0·92 [0·13]) and significantly higher than an early pandemic US population value (0·75 [0·28]; p<0·0001). Most patients had improvements in cardiac diagnostic marker and testing data at follow-up, including normal or back-to-baseline troponin concentrations (181 [91%] of 200 patients with available data), echocardiograms (262 [94%] of 279 patients), electrocardiograms (240 [77%] of 311 patients), exercise stress testing (94 [90%] of 104 patients), and ambulatory rhythm monitoring (86 [90%] of 96 patients). An abnormality was noted among 81 (54%) of 151 patients with follow-up cardiac MRI; however, evidence of myocarditis suggested by the presence of both late gadolinium enhancement and oedema on cardiac MRI was uncommon (20 [13%] of 151 patients). At follow-up, most patients were cleared for all physical activity (268 [68%] of 393 patients).

**Interpretation** After at least 90 days since onset of myocarditis after mRNA COVID-19 vaccination, most individuals in our cohort were considered recovered by health-care providers, and quality of life measures were comparable to those in pre-pandemic and early pandemic populations of a similar age. These findings might not be generalisable given the small sample size and further follow-up is needed for the subset of patients with atypical test results or not considered recovered.

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## Introduction

Evidence from the USA and multiple international vaccine safety monitoring systems support a small but increased risk of myocarditis after mRNA COVID-19 vaccination.[1] In 2021, data from the Vaccine Adverse Event Reporting System (VAERS) indicated that in US individuals aged 12 years or older, approximately 4·8 cases of myocarditis per million doses of mRNA

**CDC COVID-19 Response Team, US Centers for Disease Control and Prevention, Atlanta, GA, USA** (I Kracalik PhD, M E Oster MD, K R Broder MD, M M Cortese MD, M Glover ScD, K Shields BS, B Romanson MPH, S Novosad MD, P Marquez MSPH, J Woo MPH, A L Valderrama PhD, A Ramirez-Cardenas MPH, A Assefa MPH, J R Su MD, S S Magill MD, D K Shay MD, T T Shimabukuro MD, S V Basavaraju MD); **Children's Healthcare of Atlanta, Emory University School of Medicine, Atlanta, GA, USA** (M E Oster); **Vanderbilt University Medical Center, Nashville, TN, USA** (C B Creech MD, J Soslow MD, J M Dendy MD); **Duke Human Vaccine Institute, Durham, NC, USA** (E B Walter MD); **Duke University School of Medicine, Durham, NC, USA** (M J Campbell MD, E B Walter)

Correspondence to: Dr Ian Kracalik, CDC COVID-19 Response Team, US Centers for Disease Control and Prevention, Atlanta, GA 30329, USA nrm7@cdc.gov

## Research in context

**Evidence before this study**

In December, 2020, the US Food and Drug Administration (FDA) issued emergency use authorisations (EUAs) for the Pfizer-BioNTech COVID-19 (BNT162b2) vaccine and the Moderna COVID-19 (mRNA-1273) vaccine. In May, 2021, FDA expanded the EUA for the BNT162b2 vaccine to include adolescents aged 12–15 years. By July, 2022, more than 200 million people in the USA had received two doses of a COVID-19 mRNA vaccine and more than 1500 cases of myocarditis with onset after mRNA COVID-19 vaccination were reported to the Vaccine Adverse Events Reporting System (VAERS). We searched PubMed for articles published up to April 30, 2022, using the keywords "mRNA vaccine" and "myocarditis", without any language restrictions. Systematic reviews published in 2022 included more than 5299 individuals with myocarditis after mRNA vaccination and suggested the risk was highest in adolescents and young males after a second vaccine dose. Findings from these systematic reviews suggest that most cases of myocarditis after mRNA COVID-19 vaccination have resolution of symptoms at or soon after discharge from a short hospital stay. However, data on medium-term prognoses for adolescents and young adults diagnosed with myocarditis after mRNA COVID-19 vaccination are scarce.

**Added value of this study**

To our knowledge, this is the largest evaluation of outcomes among patients diagnosed with myocarditis after mRNA COVID-19 vaccination, with follow-up at least 90 days since onset. We collected data from both patients (or their parents or guardians) and health-care providers, and evaluated a comprehensive range of outcomes, including follow-up cardiac biomarkers, cardiac magnetic resonance imaging, echocardiograms, troponin levels, and electrocardiograms. We found that 320 (81%) of 393 patients with a health-care provider assessment were considered recovered from myocarditis, and quality of life measures were similar to pre-pandemic or early pandemic measurements. No single diagnostic test or clinical feature appeared to be associated with recovered status.

**Implications of all the available evidence**

Myocarditis after mRNA COVID-19 vaccination is rare, but potentially serious. To better understand possible longer term sequalae of myocarditis, continued follow-up is important, particularly for the patients not recovered by at least 90 days since symptom onset. Vaccination remains the most effective way of preventing morbidity and mortality from COVID-19.

COVID-19 vaccines administered were reported, with the highest reporting rates in those aged 12–29 years.[2] Despite the higher than expected occurrence of myocarditis after COVID-19 vaccination, the benefits of mRNA COVID-19 vaccines have been shown to outweigh the risk of myocarditis.[2,3]

Cardiac assessment of patients diagnosed with myocarditis after mRNA COVID-19 vaccination often shows increased cardiac biomarkers (eg, troponin concentrations) and atypical cardiac imaging (eg, echocardiograms), which are similar findings to those shown for viral or acute myocarditis.[4,5] Viral myocarditis unrelated to mRNA COVID-19 vaccination can lead to heart failure, cardiac transplantation, or death.[6] Conversely, case descriptions suggest that clinical outcomes following a diagnosis of myocarditis after mRNA COVID-19 vaccination are more favourable than those associated with viral myocarditis, with resolution of symptoms often described at or soon after discharge from a short hospital stay for myocarditis after mRNA COVID-19 vaccination.[5,7–9] However, data on follow-up prognoses for adolescents and young adults diagnosed with myocarditis after mRNA COVID-19 vaccination are scarce.[10–12] To conduct surveillance, the US Centers for Disease Control and Prevention (CDC) developed a working myocarditis case definition with a team of subspecialists that has been used in several studies.[2,5,9,13]

In August, 2021, the CDC began follow-up of myocarditis cases to describe medium-term outcomes in the age group with the highest risk of myocarditis after mRNA

COVID-19 vaccination diagnosis (ie, individuals aged 12–29 years). We report findings of clinical outcomes and quality of life at least 90 days since the onset of myocarditis after mRNA COVID-19 vaccination in adolescents and young adults aged 12–29 years.

## Methods

### Study design and population

In this follow-up surveillance study, we included US patients who were aged 12–29 years at the time of mRNA COVID-19 vaccination and for whom the time to myocarditis symptom onset was more than 90 days since vaccination and a VAERS report was filed between Jan 12, to Nov 5, 2021. VAERS is a national passive surveillance system coadministered by the CDC and the US Food and Drug Administration (FDA).[14] Any vaccine recipients, health-care providers, and vaccine providers can submit a report to VAERS. Under emergency use authorisations, vaccination providers are subject to mandatory reporting requirements for certain adverse events after COVID-19 vaccination, including hospitalisation.[15,16] The CDC encourages both vaccination providers and recipients report any clinically significant adverse event, regardless of the plausibility of the vaccine causing the event. Signs and symptoms of adverse events are coded using the Medical Dictionary for Regulatory Activities.

Physicians at the CDC reviewed all identified VAERS reports and available medical records to determine if the case met CDC case definition criteria[2] for confirmed

For more on the **Medical Dictionary for Regulatory Activities** see https://www.meddra.org
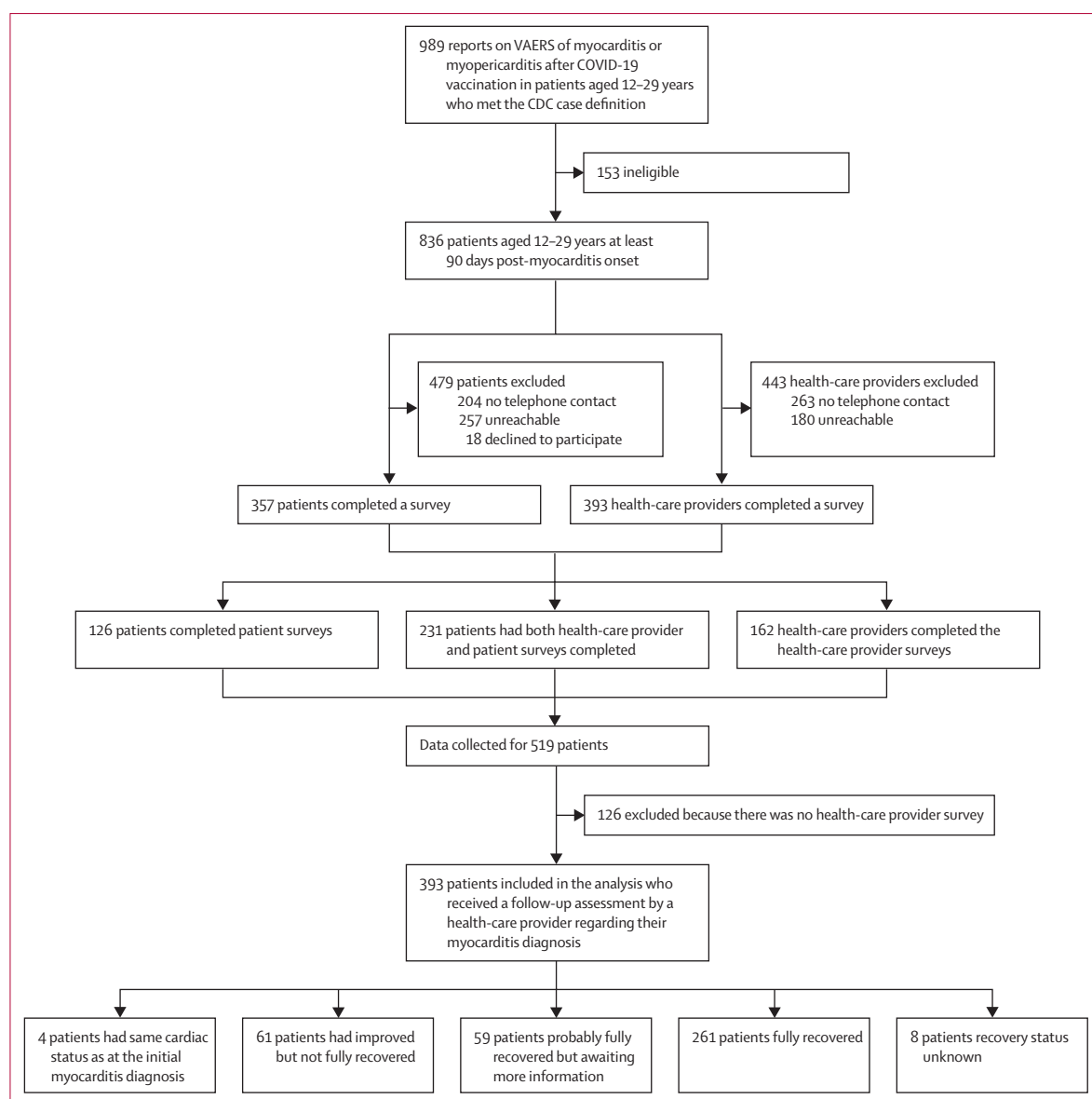
**Figure 1:** Survey participation of patients with myocarditis after mRNA COVID-19 vaccination reported to VAERS at least 90 days since symptom onset
CDC=US Centers for Disease Control and Prevention. VAERS=Vaccine Adverse Event Reporting System.

or probable myocarditis or myopericarditis (henceforth referred to as myocarditis; appendix 1 p 6).[2]

This activity was determined to meet the requirements of public health surveillance as defined in Title 45 of the Code of Federal Regulations, part 46.102(l)(2) and no institutional review board approval was needed. Verbal consent was obtained from either adult patients or parents or guardians of minor patients.

## Procedures

From Aug 24, 2021, to Jan 12, 2022, we administered a two-component telephone survey to assess patient outcomes at least 90 days since the onset of myocarditis symptoms after mRNA COVID-19 vaccination (further

details on the implementation of the survey are specified in appendix 1 [pp 2–3]). The first component administered to adult patients or to the parents or guardians of minor patients ascertained quality of life, previous medical history, need for ongoing medication for myocarditis, and presence of clinical symptoms in the 2 weeks before the date of the survey, including chest pain, shortness of breath, fatigue, and palpitations, hospitalisations, and days of school or work missed in the 2 weeks before the survey.

To assess patient quality of life and overall health after myocarditis diagnosis, we administered the EuroQol 5-dimension, 5-level (EQ-5D-5L) questionnaire that characterises health across five dimensions: mobility,

self-care, pain or discomfort, perform usual activities, and anxiety or depression.[17,18] The EQ-5D-5L instrument has been validated for use in people aged 12–29 years[19] and was used in this surveillance activity to describe the overall wellbeing of the patient group, not as an indicator of myocarditis recovery. For the quality of life questionnaire, five levels of response, from no problems to extreme problems, were dichotomised as no problems (severity level 1) or any problems (severity levels 2–5).[20] Weighted analysis converted patient responses to a numerical scale ranging from 0 (equivalent to death) to 1 (full health; appendix 1 p 7).[21] Overall health was self-rated by patients using the EuroQol visual analog scale (EQ-VAS), with scores ranging from 0 to 100 (100 representing the best possible health and 0 representing the worst possible health). We compared the patients' EQ-5D-5L survey responses with published EQ-5D-5L survey results of 18–24-year-old US population respondents before and during the COVID-19 pandemic.[22,23]

The second component of the two-part survey was a survey of health-care providers who provided care to eligible patients for this study with myocarditis after mRNA COVID-19 vaccination, which ascertained patient cardiac health and functional status (appendix 2 pp 1–19). Follow-up assessments of cardiac health after the initial myocarditis diagnosis or hospitalisation for myocarditis after COVID-19 vaccination included findings from electrocardiograms, echocardiograms, cardiac MRIs, troponin concentrations, exercise stress testing, and ambulatory rhythm monitoring (appendix 1 pp 1–2). Assessments of functional status included ongoing treat-ment or health-care provider-recommended restrictions on physical activity.

In both parts of the survey, health-care providers and patients were asked about any previous SARS-CoV-2 infection in the patient before the diagnosis of myocarditis, as determined by a positive laboratory-confirmed test; however, we did not ask about the severity of infection. To assess myocarditis recovery, health-care providers were asked the following: based on your clinical assessment and any testing information, please describe the patient's cardiac recovery status as of the date of your last visit or consultation (compared with the time of initial myocarditis diagnosis; appendix 2 p 4). Survey options were fully recovered, probably fully recovered, improved but not fully recovered, same cardiac status as at the initial diagnosis (ie, no worse or no better), worse cardiac status, unsure, or declined to answer. For this evaluation, patients determined to be fully or probably fully recovered by the health-care provider were designated recovered and patients deemed to be improved but not fully recovered or with the same cardiac status at initial diagnosis were designated not recovered. CDC's Clinical Immunization Safety Assessment (CISA) Project provided technical input for survey development.[24]

| | Patients fully or probably fully recovered (n=320) | Patients not recovered (n=65) | All patients (n=519) | p value |
|---|---|---|---|---|
| Median age, years (IQR) | 17 (15–21) | 17 (15–21) | 17 (15–22) | .. |
| Age group, years | | | | |
| 12–14 | 58 (18%) | 9 (14%) | 92 (18%) | 0.84 |
| 15–19 | 160 (50%) | 35 (54%) | 245 (47%) | .. |
| 20–24 | 69 (22%) | 15 (23%) | 120 (23%) | .. |
| 25–29 | 33 (10%) | 6 (9%) | 62 (12%) | .. |
| Sex | | | | |
| Male | 290 (91%) | 56 (86%) | 457 (88%) | 0.39 |
| Female | 30 (9%) | 9 (14%) | 61 (12) | .. |
| Unknown | 0 | 0 | 1 (<1%) | .. |
| Race, ethnicity | | | | |
| White, non-Hispanic | 182 (57%) | 32 (49%) | 274 (53%) | 0.32 |
| Asian, non-Hispanic | 16 (5%) | 1 (2%) | 25 (5%) | 0.33 |
| Black, non-Hispanic | 10 (3%) | 2 (3%) | 16 (3%) | 0.71 |
| Other race, non-Hispanic | 11 (3%) | 0 | 12 (2%) | 0.22 |
| Multiple races, non-Hispanic | 10 (3%) | 1 (2%) | 12 (2%) | 0.69 |
| American Indian or Alaskan native, non-Hispanic | 1 (<1%) | 0 | 1 (<1%) | .. |
| Hispanic | 53 (17%) | 14 (22%) | 98 (19%) | 0.33 |
| Unknown | 37 (12%) | 13 (20%) | 81 (16%) | .. |
| Previous SARS-CoV-2 infection* | 28 (9%) | 4 (6%) | 48 (9%) | 0.61 |
| Received two COVID-19 vaccine doses | 278 (87%) | 58 (89%) | 448 (86%) | 0.75 |
| Underlying medical condition | | | | |
| At least one condition, excluding obesity | 63 (20%) | 16 (25%) | 99 (19%) | 0.46 |
| Asthma† | 29 (9%) | 4 (6%) | 41 (8%) | 0.60 |
| Autoimmune disease | 10 (3%) | 1 (2%) | 13 (3%) | 0.69 |
| Arrhythmia | 9 (3%) | 1 (2%) | 16 (3%) | 0.86 |
| Congenital heart disease | 8 (2%) | 2 (3%) | 10 (2%) | 0.68 |
| Genetic or chromosomal | 7 (2%) | 8 (12%) | 15 (3%) | 0.0005 |
| Previous heart failure | 1 (<1%) | 1 (2%) | 2 (<1%) | 0.31 |
| Kawasaki disease | 1 (<1%) | 0 | 2 (<1%) | .. |
| Myocarditis | 4 (1%) | 1 (2%) | 7 (1%) | .. |
| Type 1 diabetes | 1 (<1%) | 1 (2%) | 3 (1%) | 0.31 |
| BMI-based obesity‡ | 80/291 (27%) | 16/63 (25%) | 99/359 (28%) | 0.86 |

(Table 1 continues on next page)

## Statistical analysis

To assess non-response bias, demographic and clinical characteristics of survey respondents were compared with characteristics of non-respondents (eg, those who were unreachable), including age, sex (male or female), self-reported race and ethnicity, geographical census region, and findings from initial echocardiograms (appendix 1 p 8). Additionally, we compared VAERS reporter type (health-care provider or patient), geographical census region, age, sex, initial echocardiogram findings, and race and ethnicity among survey respondents and non-respondents.

See Online for appendix 2

| | Patients fully or probably fully recovered (n=320) | Patients not recovered (n=65) | All patients (n=519) | p value |
|---|---|---|---|---|
| (Continued from previous page) | | | | |
| Patient-reported symptoms in the patient survey | n=195§ | n=28§ | n=357 | .. |
| At least one symptom | 94 (48%) | 18 (64%) | 178 (50%) | 0·16 |
| Chest pain or discomfort | 55 (28%) | 13 (46%) | 113 (32%) | 0·082 |
| Chest pain or discomfort while resting | 45 (23%) | 11 (39%) | 92 (26%) | 0·011 |
| Fatigue | 40 (21%) | 12 (43%) | 89 (25%) | 0·018 |
| Fatigue while resting | 28 (14%) | 10 (36%) | 63 (18%) | 0·012 |
| Shortness of breath | 38 (19%) | 9 (32%) | 80 (22%) | 0·28 |
| Shortness of breath while resting | 15 (8%) | 4 (14%) | 38 (11%) | 0·42 |
| Heart palpitations | 36 (18%) | 6 (21%) | 77 (22%) | 0·71 |
| Heart palpitations while resting | 28 (14%) | 5 (18%) | 59 (17%) | 0·84 |

Data are n (%) unless specified otherwise. Data are based on the completion of 357 patient surveys, 393 provider surveys, and 231 linked surveys, resulting in 519 patients for which data were collected. Health-care provider determination of patient myocarditis recovery was provided for 393 patients, of whom 320 were considered fully or probably fully recovered and 65 were not considered recovered (and eight patients had an undetermined recovery status; figure 1). Based on the last patient encounter, health-care providers reported that 62 (16%) of 393 patients had at least one symptom that might occur with myocarditis. *Previous SARS-CoV-2 infection before the diagnosis of myocarditis, as determined by a positive laboratory-confirmed test; the interval from a positive SARS-CoV-2 test result to mRNA COVID-19 vaccination was a median of 139 days (IQR 92–198; n=15 with a date provided). †Asthma, for which prescription medicine within the past 2 years was needed; if asthma was only with exercise, it was not recorded. ‡BMI was calculated using measurements obtained at the earliest follow-up visit: the formula weight (pounds)/[height (inches)]² ×703. The denominators reflect the number of individuals with data available to calculate BMI. §All patients who self-reported symptoms in the patient survey and had a provider-reported recovery status.

*Table 1:* Demographic characteristics and symptoms of patients by provider-reported recovery status from myocarditis after mRNA COVID-19 vaccination

Descriptive analyses were conducted to determine frequencies, percentages, means, and SDs to characterise cases of myocarditis after mRNA COVID-19 vaccination by age, sex, time elapsed since symptom onset, quality of life measures, and clinical outcome. All cases meeting the CDC definition for myocarditis were included, regardless of whether a suspected alternative cause was identified. For assessment of recovery status, we conducted a sensitivity analysis limited to individuals with symptom onset at least 7 days after vaccination and without a suspected alternative cause identified by their health-care provider (appendix 1 p 4). Missing values were not imputed. To assess statistical significance of comparisons, we used the χ² test for categorical variables, Fisher's exact test for variables with small sample sizes (n<5), and the Student's t-test or the Mann–Whitney U test for continuous variables. All analyses were performed with R software (version 4.1.1). p<0·05 was considered to be statistically significant.

### Role of the funding source
The funder led data collection, data analysis, data interpretation, writing, and submission of the manuscript.

## Results
Between Jan 12 and Nov 5, 2021, 989 cases of myocarditis after mRNA COVID-19 vaccination in patients aged 12–29 years were reported to VAERS and met the CDC's case definition for myocarditis. Of these, 836 (85%) patients were at least 90 days post-myocarditis onset (figure 1). Of the 836 patients, 204 (24%) patients had no telephone number available for contact and 257 (31%) patients were unreachable. Of the remaining 375 patients, 357 (95%) patients consented to the survey and 18 (5%) patients declined. Between Aug 24, 2021, and Jan 12, 2022, we contacted and collected data for 519 (62%) of the 836 eligible patients: 126 patients via patient survey only, 162 patients via health-care provider survey only, and 231 patients via both the patient and health-care provider survey (figure 1). Median interval from myocarditis onset to survey completion was 143 days (IQR 131–162) for patients and 191 days (170–216) for health-care providers. We found no significant differences in VAERS reporter type (health-care provider or patient), geographical census region, age, sex, initial echocardiogram findings, or race or ethnicity in patients surveyed compared with patients who were not surveyed (appendix 1 p 8). In a subset of patients with abnormal echocardiograms, the abnormality identified was a left ventricular ejection fraction (LVEF) of less than 50%. Of the 100 survey respondents with LVEF values recorded at their initial diagnosis, 33 (33%) had LVEF values less than 50%, which was not statistically different from the results in non-respondents (27 [42%] of 65 non-respondents; χ²=1·24, p=0·265).

For 393 (47%) of 836 patients, health-care providers were contacted; 241 (61%) of 393 were cardiologists. At the time of the survey, health-care providers considered 320 (81%) of 393 patients to be recovered: 261 (66%) patients were considered fully recovered and 59 (15%) patients were considered to be probably recovered but awaiting further information. An additional 61 (16%) patients had improved and four patients had the same cardiac status as at the initial myocarditis diagnosis; these 65 patients were categorised as not fully recovered (figure 1). The cumulative proportion of patients considered recovered in the time (weeks) since the last health-care provider encounter is shown in appendix 1 (p 15). The median time from myocarditis symptom onset to the last health-care provider encounter for patients who were considered probably fully recovered or fully recovered was 92 days (IQR 43–133), and for patients who were considered fully recovered the median time was 84 days (36–135).

Most patients were male (457 [88%] of 519 patients) and White non-Hispanic (274 [53%]), and the median age of all patients was 17 years (IQR 15–22; table 1). 98 (19%) of 519 patients were Hispanic of any race. There was no notable difference between recovered individuals compared with individuals who were not recovered across any ethnic or racial groups. Overall, patients considered to be recovered and not recovered from myocarditis were similar with respect to age

(median age 17 years [IQR 15–21] for patients considered recovered *vs* 17 years [15–21] for those considered not recovered) and sex (290 [91%] male individuals who were considered recovered *vs* 56 [86%] of male individuals who were considered not to be recovered, and 30 [9%] female individuals who were considered recovered *vs* 9 [14%] of female individuals who were not considered recovered). The median time from illness onset to health-care provider interview for the 320 (81%) of 393 individuals who were considered recovered was 189 days (IQR 167–214), and for the 61 (16%) of 393 patients who were considered improved but not fully recovered the median time was 195 days (179–195).

In the 2 weeks before the survey date, 178 (50%) of 357 patients reported having at least one symptom that might occur with myocarditis (chest pain or discomfort, fatigue, shortness of breath, or palpitations). Patients who were not considered recovered from myocarditis more frequently reported fatigue than did patients who were considered recovered (12 [43%] *vs* 40 [21%]; p=0·018; table 1). By contrast, based on the last patient encounter, health-care providers reported that 62 (16%) of 393 patients at least one symptom that might occur with myocarditis (table 1).

Of 357 patients surveyed, 267 (75%) were enrolled in school or in paid employment; 43 (16%) of whom reported missing school or workdays in the 2 weeks before the survey date. Of those 43 patients, 15 (35%) believed it was associated with myocarditis.

Of 357 patients surveyed, 249 (71%) consented to completing both the EQ-5D-5L and EQ-VAS components of the patient survey. Of 249 patients, four (2%) reported problems with self-care, 13 (5%) with mobility, 49 (21%) with performing usual activities, 74 (30%) with pain, and 114 (46%) with anxiousness or depression (figure 2A). Overall, patients reported having good health, reflected by the high median weighted index score (0·94; IQR 0·88–1·00) and median overall health status (EQ-VAS) score (90; 80–95; figure 2B, C).

The mean EQ-5D-5L weighted utility score in our group (0·91 [SD 0·13]) was significantly higher than that for US respondents aged 18–24 years who completed a EQ-5D-5L questionnaire during the pandemic, as reported by Hay and colleagues[22] (0·75 [0·28]; p<0·0001). Mean EQ-5D-5L weighted utility scores from the pre-pandemic timepoint among US respondents aged 18–24 years have also been reported by Jiang and colleagues, from face-to-face surveys and online surveys.[23] The weighted score from our survey was not significantly different to that obtained in the face-to-face surveys (0·92 [0·13]), but our score was significantly higher than that from the online surveys (0·84 [0·18]; p<0·0001).

Most patients were admitted to hospital after an initial diagnosis of myocarditis (484 [93%] of 519 patients). Of these 484 patients, 393 (81%) patients had information on level of care, according to the health-care provider surveys; 99 (25%) of these 393 patients were treated in an intensive
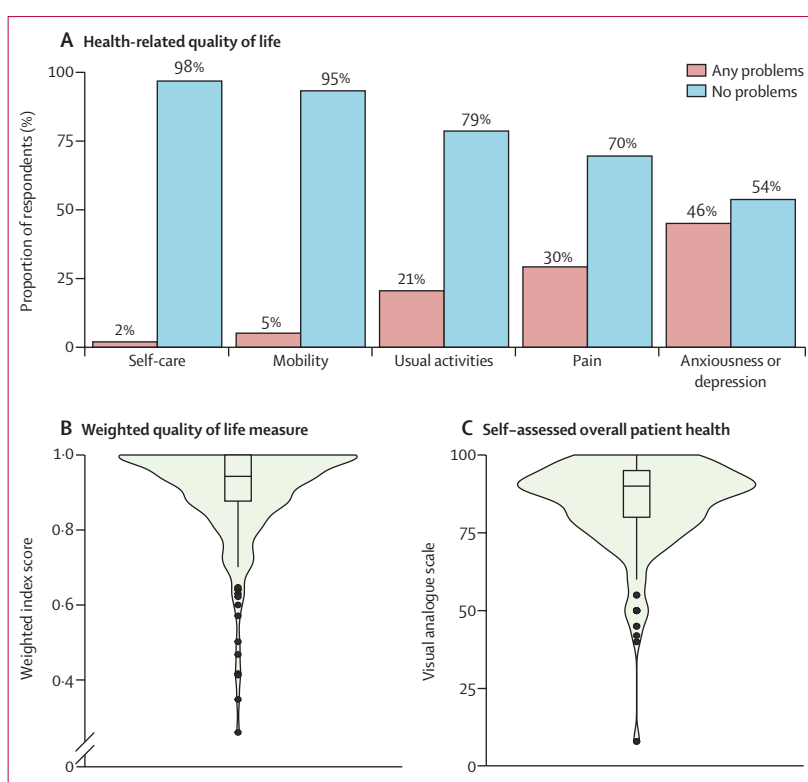


Figure 2: Self-assessment of health-related quality of life among patients with myocarditis after mRNA COVID-19 vaccination
(A) Bar plot of health-related quality of life among patients. Patients were administered the EuroQol 5-dimension 5-severity level questionnaire; for analysis, the five health-related dimensions were dichotomised into the frequency of problems (severity levels 2–5) and no problems (level 1). (B) Violin plot of weighted quality of life measure (using value weights in appendix 1 p 7) converted from each patient health profile from (A) to an index score between 1 (perfect health) and 0 (equivalent to death). (C) Violin plot of patient self-assessed overall health on a scale from 0 to 100 (with 100 representing best possible health and 0 representing the worst possible health). The denominator for the EuroQol questionnaire was 249 respondents. In the violin plots (B, C), the limits of the boxes denote IQR and the horizontal line denotes median values. Whisker endpoints are equal to the maximum and minimum values below or above the median plus or minus 1·5 times the IQR. The width of the outer shape around the box plots indicates the probability density of values or responses with a given result.

care unit and one (<1%) patient required extracorporeal membrane oxygenation (table 2). To our knowledge, no deaths occurred during follow-up among the patients eligible for the survey. Six (2%) of 357 patients who self-reported re-admission to hospital had a hospital admission because of an adverse event after myocarditis treatment (n=3; adverse reactions to intravenous immune globulin) or had any cardiac abnormality identified (n=3; appendix 1 p 6); all patients were discharged within 1 week.

At follow-up, fewer patients had restrictions on physical activity than at initial diagnosis, and 34 (52%) of 65 individuals with restrictions on physical activity at the time of follow-up who were not considered recovered were cleared for all physical activity; 31 (48%) individuals still had restrictions (table 2). Median interval from myocarditis onset to approval for all physical activity was 98 days (IQR 57–134; table 2).

104 (26%) of 393 patients were prescribed daily medications related to myocarditis at the last

| | Patients fully or probably fully recovered (n=320) | Patients not recovered (n=65) | Patient recovery unknown (n=8) | p value |
|---|---|---|---|---|
| **Highest level of care** | | | | |
| Hospitalised with no intensive care | 210 (66%) | 40 (62%) | 4 (50%) | 0·66 |
| Hospitalised with intensive care | 85 (27%) | 12 (18%) | 2 (25%) | 0·22 |
| Not hospitalised, managed as outpatient | 14 (4%) | 9 (14%) | 2 (25%) | 0·0074 |
| Intensive care with ECMO | 0 | 1 (2%) | 0 | .. |
| Unknown* | 11 (3%) | 3 (5%) | 0 | .. |
| **Patient restrictions on physical activity** | | | | |
| At time of initial myocarditis hospitalisation or diagnosis | 267 (83%) | 53 (82%) | 6 (75%) | 0·84 |
| At time of last health-care provider follow-up | 91 (28%) | 31 (48%) | 3 (38%) | 0·0038 |
| Cleared for physical activity and date of clearance known | 160/267 (60%) | 16/53 (30%) | 2/6 (33%) | 0·026 |
| Median days from myocarditis onset to physical activity clearance (IQR) | 104 (63–135) | 114 (73–156) | 80 | 0·12 |
| **Patient cardiac MRI** | | | | |
| At time of initial myocarditis hospitalisation or diagnosis | 137 (43%) | 32 (49%) | 0 | 0·56 |
| At time of healthcare provider follow-up | 114 (36%) | 36 (55%) | 1 (13%) | 0·0023 |
| **Patient echocardiogram** | | | | |
| At time of initial myocarditis hospitalisation or diagnosis | 257 (80%) | 55 (85%) | 7 (88%) | 0·53 |
| At time of health care provider follow-up | 230 (72%) | 51 (78%) | 3 (38%) | 0·35 |
| **Patient troponin** | | | | |
| At time of initial myocarditis hospitalisation or diagnosis | 318 (99%) | 65 (100%) | 7 (88%) | 0·76 |
| At time of healthcare provider follow-up | 166 (52%) | 33 (51%) | 1 (13%) | 0·86 |
| **Patient electrocardiogram** | | | | |
| At time of initial myocarditis hospitalisation or diagnosis | 210 (66%) | 34 (52%) | 6 (75%) | 0·059 |
| At time of health-care provider follow-up | 251 (78%) | 55 (85%) | 5 (63%) | 0·34 |
| **Patient exercise stress test** | | | | |
| At time of health-care provider follow-up | 91 (28%) | 16 (25%) | 2 (25%) | 0·63 |
| **Patient ambulatory rhythm monitoring** | | | | |
| At time of health-care provider follow-up | 86 (27%) | 18 (28%) | 1 (13%) | 0·89 |
| Prescribed medication at last provider follow-up | 68 (21%) | 33 (51%) | 3 (38%) | <0·0001 |
| **Daily medication types prescribed†** | | | | |
| Colchicine | 31 (10%) | 17 (26%) | 0 | 0·0005 |
| β-blocker | 29 (9%) | 12 (18%) | 1 (13%) | 0·043 |
| Non-steroidal anti-inflammatory | 21 (7%) | 9 (14%) | 1 (13%) | 0·081 |
| Aspirin | 9 (3%) | 5 (8%) | 1 (13%) | 0·069 |
| | | | | (Table 2 continues on next page) |

health-care provider encounter (table 2). Patients who were not considered recovered from myocarditis were more frequently prescribed daily medication than were patients who were considered to be recovered. The most prescribed medications, as of the last health-care provider follow-up, were colchicine, β-blockers, and non-steroidal anti-inflammatory drugs (table 2).

At follow-up, most patients had improvements in diagnostic marker and imaging data, including normal or back-to-baseline troponin concentrations, echocardiograms, exercise stress testing, ambulatory rhythm monitoring, and electrocardiograms (figure 3). In the ten patients with abnormal ambulatory rhythm monitoring results, we found eight (80%) had atrial, supraventricular, or ventricular arrhythmia, three (30%) had a conduction delay or block, and five (50%) had frequent atrial or ventricular ectopy. Of these 10 patients, three (30%) had evidence of late gadolinium enhancement on follow-up cardiac MRI; of the three with evidence of late gadolinium enhancement, two (67%) had evidence of an atrial, supraventricular, or ventricular arrhythmia. Among the 151 patients who had cardiac MRIs during outpatient follow-up, 81 (54%) patients had one or more abnormalities. Abnormal cardiac MRI findings included the presence of late gadolinium enhancement (71 [47%] patients), inflammation or oedema (22 [15%] patients), or wall motion abnormalities (six [4%] patients; figure 3, appendix 1 p 9). Evidence of ongoing myocarditis, defined by both late gadolinium enhancement and oedema using modified Lake Louise criteria,[25] was uncommon (20 [13%] of 151 patients; appendix 1 p 9). Median interval from symptom onset to evidence of ongoing myocarditis was 26 days (IQR, 9–94) and from symptom onset to evidence of late gadolinium enhancement was 109 days (58–163; appendix 1 p 10). Of the 67 patients with late gadolinium enhancement or evidence of ongoing myocarditis, additional follow-up testing indicated abnormal echocardiograms in five (7%) patients, abnormal troponin concentrations in five (7%) patients, and abnormal electrocardiograms in 14 (21%) patients (appendix 1 p 13).

In the subset of patients with abnormal findings at the time of myocarditis diagnosis, abnormal diagnostic markers or abnormal imaging were also observed at follow-up in seven (12%) of 60 with initial abnormal echocardiograms, 19 (5%) of 387 with initial elevated troponin levels, and 47 (32%) of 146 with initial abnormal cardiac MRIs (figure 4). There was substantial heterogeneity in cardiac biomarkers, imaging, and patient functional status between patients considered recovered or not recovered from myocarditis (appendix 1 p 16). All cardiac test results (ie, echocardiogram, electrocardiogram, cardiac MRI, and troponin) were available for follow-up review in only 199 (62%) of 320 patients considered recovered, 44 (68%) of 65 considered not recovered, and three (38%) of eight with an unknown recovery status.

## Discussion

We ascertained outcomes at least 90 days since onset of myocarditis among 519 patients aged 12–29 years who received an mRNA COVID-19 vaccination and met the CDC case definition for myocarditis. Most (81%) patients for whom a follow-up health-care provider survey was completed were considered recovered from myocarditis, and most self-reported overall good health on the EQ-5D-5L. Readmissions to hospital were uncommon, and no deaths were identified during the follow-up period. Myocarditis after mRNA COVID-19 vaccination is rare yet potentially serious, and although most patients were considered recovered by health-care providers at least 90 days since onset, nearly half of patients continued to self-report symptoms, including chest pain, and a quarter were prescribed daily cardiac medications. These findings suggest that continued follow-up and assessment of myocarditis after mRNA COVID-19 vaccination is needed to more fully understand recovery after vaccine-associated myocarditis.

From a clinical standpoint, our findings suggest that myocarditis after mRNA COVID-19 vaccination could have a more favourable prognosis than myocarditis after viral infection, based on data available from the pre-COVID-19 period. In a published study of outcomes in children within 90 days of viral or acute myocarditis onset in the USA, 119 (23%) of 514 individuals required extracorporeal membrane oxygenation or a ventricular-assisted device and 58 (11%) of 514 individuals required cardiac transplant or died.[6] In a recent nationwide study in Denmark of adults, 90-day all-cause mortality among those with acute myocarditis was 4·9%.[26] A longer term follow-up study of acute myocarditis among older adults (median age 34 years [IQR 24–42]) in Italy observed cardiac mortality or heart transplant rates at 1 year and 5 years of 3·0% and 4·1%, respectively, although complicated cases had rates of adverse cardiac outcomes that were several times higher.[27] In contrast with these studies, we found that only four (1%) patients had the same cardiac status as at the initial myocarditis diagnosis (ie, did not improve but did not worsen), whereas more than 95% (381 of 393 patients) showed improvement or recovery. Consistent with our findings, a recent report comparing classic myocarditis to COVID-19 vaccine-related myocarditis in individuals aged younger than 21 years observed similar clinical presentations and found COVID-19 vaccine-related myocarditis had better outcomes and a more rapid cardiac recovery.[28]

Published data for health-related quality of life in the USA among individuals aged 18–24 years, before the COVID-19 pandemic, showed that 45 (42%) of 107 individuals reported anxiety or depression and 35 (33%) of 107 individuals reported pain or discomfort.[23] More recent quality of life measure data from Hay and colleagues[22] among US respondents during the early stages of the COVID-19 pandemic showed that

| | Patients fully or probably fully recovered (n=320) | Patients not recovered (n=65) | Patient recovery unknown (n=8) | p value |
|---|---|---|---|---|
| (Continued from previous page) | | | | |
| Angiotensin-converting enzyme inhibitor | 8 (3%) | 6 (9%) | 0 | 0·018 |
| Diuretic | 3 (1%) | 3 (5%) | 0 | 0·063 |
| Corticosteroid | 1 (<1%) | 3 (5%) | 0 | 0·016 |
| Angiotensin II receptor blocker | 2 (1%) | 7 (11%) | 0 | <0·0001 |
| Other medication | 3 (1%) | 2 (3%) | 1 (13%) | 0·19 |

Data are n (%) unless otherwise specified. Data are based on the completion of 393 health-care provider surveys. Health-care provider determination of patient myocarditis recovery was provided for 393 patients, of whom 320 were considered fully or probably fully recovered, 65 were not considered recovered, and the health-care provider was unsure of the recovery status in eight patients, as shown in figure 1. Follow-up cardiac testing was performed, although the result of the test was not available for troponin concentration in three patients, echocardiogram in five patients, cardiac MRI in seven patients, exercise stress testing in five patients, and ambulatory rhythm monitoring in nine patients. ECMO=extracorporeal membrane oxygenation. *Some data were unknown because not all health-care providers who were surveyed knew the level of care the patient received as not all cared for the patient while they were in the hospital. †The denominator is based on patients who, as of their last health-care provider encounter, were recommended to use daily medication.

*Table 2*: Level of care, testing, and treatment by recovery status among patients with myocarditis after mRNA COVID-19 vaccination

1653 (60·2%) of 2746 individuals reported anxiety or depression.[22] Consistent with these observations, we found that patients with myocarditis after mRNA COVID-19 vaccination reported similar or better quality of life measures than the general US population, with fewer patients with myocarditis reporting anxiety or depression than did individuals during the pandemic (46% [114/249] vs 60·2% [1653/2746]). However, absence of age-specific data in the previous analyses[22,23] precluded any further statistical comparisons in this study.

Despite clinical improvements and normalisation of most diagnostic test results, as noted by health-care providers, half of patients (178/357) surveyed continued to report at least one symptom potentially associated with myocarditis after COVID-19 vaccination. One possible explanation for the persistence of symptoms is that approximately 50% of patients reported depression or anxiety, conditions that can manifest as symptoms associated with myocarditis, such as chest pain or palpitations.[29]

The meaning of the cardiac MRI findings among the subset of patients who received cardiac imaging is unclear. Evidence of ongoing myocarditis on follow-up cardiac MRIs based on modified Lake Louise criteria[25] was uncommon. However, consistent with the few published case series of myocarditis after mRNA COVID-19 vaccination, we observed that nearly half of patients (71/151) with follow-up cardiac MRIs had residual late gadolinium enhancement, suggestive of myocardial scarring.[10–12,25] We did not note the degree of late gadolinium enhancement identified during follow-up, but a recent study that assessed serial cardiac MRIs in patients younger than 19 years with myocarditis after COVID-19 vaccination and persistent late gadolinium enhancement showed improvement over
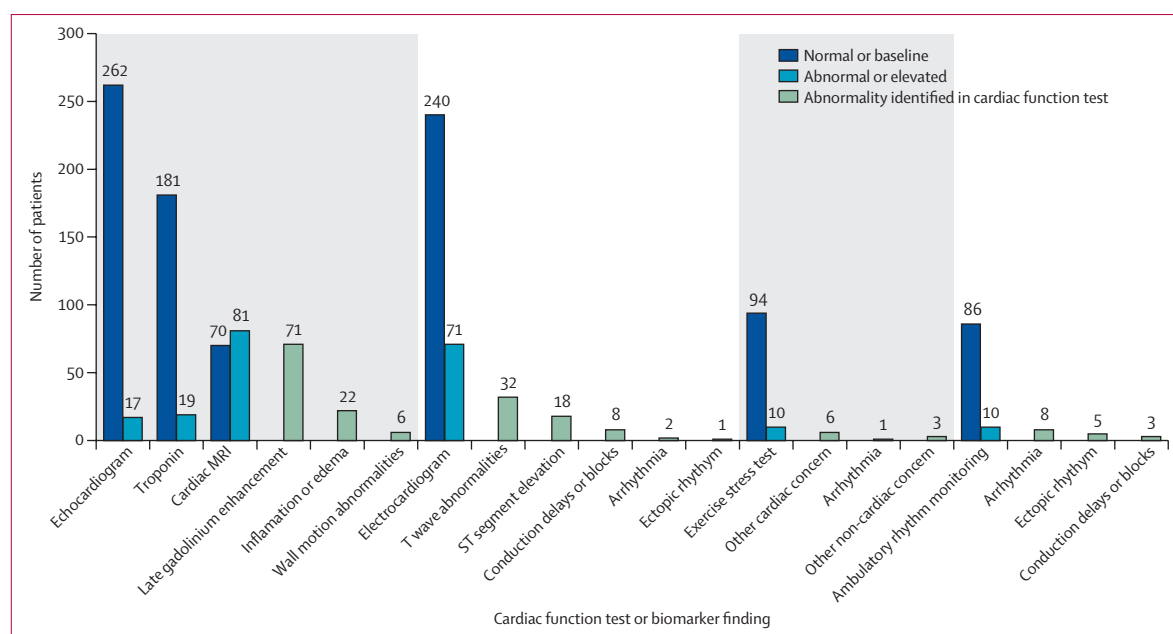
**Figure 3: Follow-up functional status, biomarker testing, and cardiac imaging in patients at least 90 days since onset of myocarditis after mRNA COVID-19 vaccination**

Cardiac biomarker testing or imaging findings are from the health-care provider surveys completed for 393 patients. Not all patients received diagnostic testing or imaging and the denominator for each follow-up test is equal to the sum of the normal and abnormal findings; the type of abnormalities identified are not mutually exclusive.
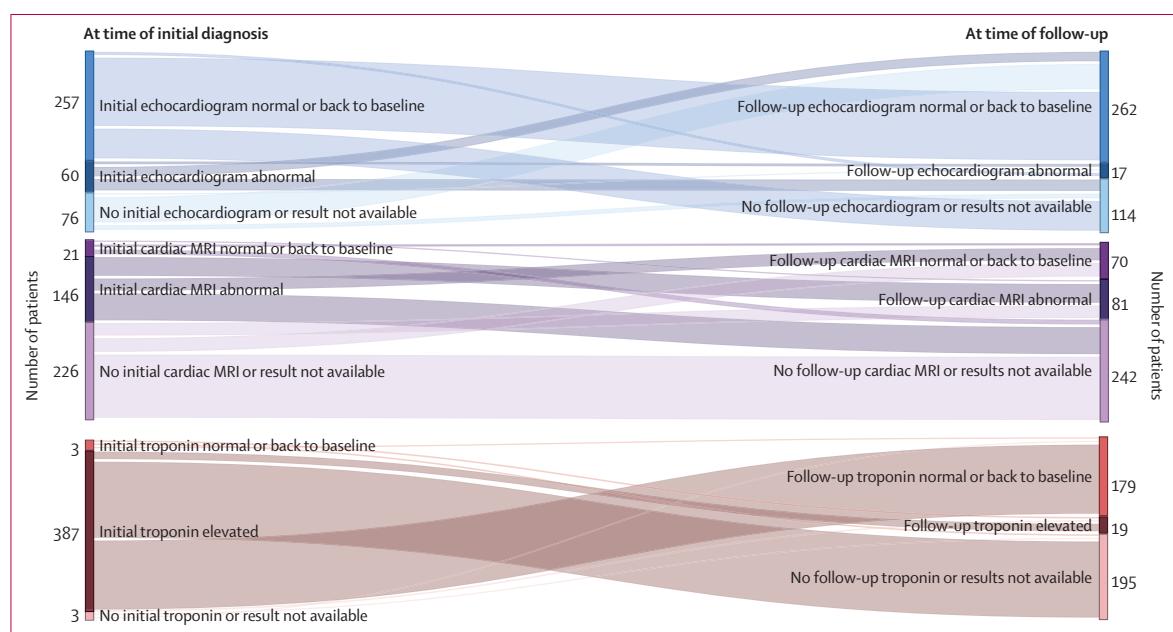


**Figure 4: Changes in cardiac biomarker and imaging from the initial encounter and the health-care provider follow-up**

Testing, including echocardiograms, cardiac MRIs, and troponin concentrations, performed at the time of initial myocarditis diagnosis and at follow-up are not necessarily matched because each patient had testing (or not) at the discretion of the treating health-care providers.

time.[30] In a small subset of patients, initial cardiac imaging at diagnosis was normal but follow-up imaging was abnormal. It is possible that clinical findings in these patients continued to evolve after diagnosis. Another possibility is that the initial and follow-up imaging results were evaluated by different health-care providers, who had varying interpretations.

In previous studies during the pre-COVID era, cardiac scarring related to myocarditis on follow-up MRI was not uncommon, yet its clinical significance has remained

controversial.[10,31–33] Although late gadolinium enhancement during the acute episode of myocarditis has been shown in children and adults to be a possible indication of future adverse cardiac events, including arrythmias, extracorporeal membrane oxygenation, transplantation, and death,[31,34–36] the importance of late gadolinium enhancement noted on follow-up cardiac MRIs in patients with viral myocarditis is unclear.[31] Indeed, guidelines regarding clearance of athletes for competitive sports after myocarditis acknowledge the unclear role of cardiac MRI in the follow-up of such patients.[37]

Our follow-up evaluation is subject to several limitations. First, and most importantly, the absence of clear clinical practice guidelines for the outpatient follow-up of myocarditis meant that comparing clinical course among patients was challenging, as no standard level of care was provided. Therefore, some data pertinent to understanding potential residual symptoms and disease were unavailable. We found substantial heterogeneity in the initial evaluation and follow-up of patients, particularly in the cardiac diagnostic imaging received. Current guidelines recommend restricting patients with myocarditis (eg, athletes) from competitive sports for 3–6 months,[38] although we noted some variability among health-care providers in clearing patients for a return to all physical activity. There are no standard criteria for myocarditis recovery, and we did not identify any clinical feature or diagnostic test results associated with recovery status in the patients we evaluated. Forthcoming expert guidelines regarding the follow-up management and testing of patients with myocarditis could help standardise care in the future.

A second limitation is the passive (or spontaneous) nature of VAERS reporting. Some US cases of myocarditis associated with mRNA COVID-19 vaccination will not have been reported; however, it is unclear how cases reported or not reported initially to VAERS could differ. Selection bias is a possible limitation in any survey activity. Third, although 519 (62%) of the 836 eligible patients with myocarditis who filed a report to VAERS were included in this follow-up evaluation, 275 (33%) declined to participate or were unreachable. Reassuringly, we found no significant differences in the age, sex, race, or census region of respondents compared with non-respondents, although our findings might not be generalisable to all US individuals aged 12–29 years who develop myocarditis after mRNA COVID-19 vaccination due to the small sample size. Fourth, we relied on health-care provider reports for all diagnostic data results. Unlike prospective studies, we did not have access to central interpretation of tests (eg, electrocardiograms, echocardiograms, and cardiac MRIs). Although this limitation probably introduces some variability into the findings, it also reflects real-world practice and data appeared not to be missing at random. A fifth limitation is the absence of a control group for the analysis of patient symptoms. Control groups are

important for contextualising symptoms. For example, in a study of long COVID among children and adolescents (aged <21 years) in the USA, Rao and colleagues[39] found that 41·9% of patients with a history of COVID-19 reported at least one symptom of post-acute sequelae of SARS-CoV-2 infection, as did 38·2% of a control group without a history of COVID-19. Although no pre-myocarditis measures were available for our group of patients with myocarditis, we found that quality of life measures among those with COVID-19 vaccine-associated myocarditis at follow-up were similar to or better than those of contemporary populations studied before or early in the pandemic.[22,23] Finally, given limitations on the ability to determine causes of myocarditis other than mRNA vaccination, we included all cases in our analyses.

In summary, after at least 90 days since onset of myocarditis after mRNA COVID-19 vaccination, 81% of patients were considered recovered by their health-care provider. At the time of follow-up, these patients reported quality of life measures similar to pre-pandemic reports among individuals of similar ages in the USA. 50% of patients reported at least one symptom at follow-up. Among a subset of 151 patients who had follow-up cardiac MRI results, 54% had an abnormal finding. The CDC is conducting additional follow-up on patients who were not considered recovered at least 12 months since symptom onset, to better understand their longer term outcomes.

conclusions in this Article are those of the authors and do not necessarily represent the official position of the CDC. Mention of a product or company name is for identification purposes only and does not constitute endorsement by the CDC.

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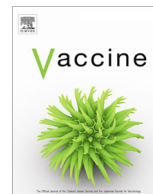
# Serious adverse events of special interest following mRNA COVID-19 vaccination in randomized trials in adults

Joseph Fraiman [a], Juan Erviti [b], Mark Jones [c], Sander Greenland [d], Patrick Whelan [e], Robert M. Kaplan [f], Peter Doshi [g,*]

[a] Thibodaux Regional Health System, Thibodaux, LA, USA
[b] Unit of Innovation and Organization, Navarre Health Service, Spain
[c] Institute of Evidence-Based Healthcare, Bond University, Gold Coast, QLD, Australia
[d] Fielding School of Public Health and College of Letters and Science, University of California, Los Angeles, CA, USA
[e] Geffen School of Medicine, University of California, Los Angeles, CA, USA
[f] Clinical Excellence Research Center, School of Medicine, Stanford University, CA, USA
[g] School of Pharmacy, University of Maryland, Baltimore, MD, USA

## ARTICLE INFO

## ABSTRACT

*Introduction:* In 2020, prior to COVID-19 vaccine rollout, the Brighton Collaboration created a priority list, endorsed by the World Health Organization, of potential adverse events relevant to COVID-19 vaccines. We adapted the Brighton Collaboration list to evaluate serious adverse events of special interest observed in mRNA COVID-19 vaccine trials.
*Methods:* Secondary analysis of serious adverse events reported in the placebo-controlled, phase III randomized clinical trials of Pfizer and Moderna mRNA COVID-19 vaccines in adults (NCT04368728 and NCT04470427), focusing analysis on Brighton Collaboration adverse events of special interest.
*Results:* Pfizer and Moderna mRNA COVID-19 vaccines were associated with an excess risk of serious adverse events of special interest of 10.1 and 15.1 per 10,000 vaccinated over placebo baselines of 17.6 and 42.2 (95 % CI −0.4 to 20.6 and −3.6 to 33.8), respectively. Combined, the mRNA vaccines were associated with an excess risk of serious adverse events of special interest of 12.5 per 10,000 vaccinated (95 % CI 2.1 to 22.9); risk ratio 1.43 (95 % CI 1.07 to 1.92). The Pfizer trial exhibited a 36 % higher risk of serious adverse events in the vaccine group; risk difference 18.0 per 10,000 vaccinated (95 % CI 1.2 to 34.9); risk ratio 1.36 (95 % CI 1.02 to 1.83). The Moderna trial exhibited a 6 % higher risk of serious adverse events in the vaccine group: risk difference 7.1 per 10,000 (95 % CI −23.2 to 37.4); risk ratio 1.06 (95 % CI 0.84 to 1.33). Combined, there was a 16 % higher risk of serious adverse events in mRNA vaccine recipients: risk difference 13.2 (95 % CI −3.2 to 29.6); risk ratio 1.16 (95 % CI 0.97 to 1.39).
*Discussion:* The excess risk of serious adverse events found in our study points to the need for formal harm-benefit analyses, particularly those that are stratified according to risk of serious COVID-19 outcomes. These analyses will require public release of participant level datasets.

## 1. Introduction

In March 2020, the Brighton Collaboration and the Coalition for Epidemic Preparedness Innovations partnership, Safety Platform for Emergency vACcines (SPEAC), created and subsequently updated a "priority list of potential adverse events of special interest relevant to COVID-19 vaccine trials." [1] The list comprises adverse events of special interest (AESIs) based on the specific vaccine platform, adverse events associated with prior vaccines in general, theoretical associations based on animal models, and COVID-19 specific immunopathogenesis. [1] The Brighton Collaboration is a global authority on the topic of vaccine safety and in May 2020, the World Health Organization's Global Advisory Committee on Vaccine Safety endorsed and recommended the reporting of AESIs based on this priority list. To our knowledge, however, the list has not been applied to serious adverse events in randomized trial data.

* Corresponding author at: Peter Doshi, 220 N Arch Street, Baltimore, MD 21201, USA.
*E-mail addresses:* josephfraiman@gmail.com (J. Fraiman), jervitil@navarra.es (J. Erviti), majones@bond.edu.au (M. Jones), lesdomes@g.ucla.edu (S. Greenland), PWhelan@mednet.ucla.edu (P. Whelan), Bob.Kaplan@stanford.edu (R.M. Kaplan), pdoshi@rx.umaryland.edu (P. Doshi).

We sought to investigate the association between FDA-authorized mRNA COVID-19 vaccines and serious adverse events identified by the Brighton Collaboration, using data from the phase III randomized, placebo-controlled clinical trials on which authorization was based. We consider these trial data against findings from post-authorization observational safety data. Our study was not designed to evaluate the overall harm-benefit of vaccination programs so far. To put our safety results in context, we conducted a simple comparison of harms with benefits to illustrate the need for formal harm-benefit analyses of the vaccines that are stratified according to risk of serious COVID-19 outcomes. Our analysis is restricted to the randomized trial data, and does not consider data on post-authorization vaccination program impact. It does however show the need for public release of participant level trial datasets.

## 2. Methods

Pfizer and Moderna each submitted the results of one phase III randomized trial in support of the FDA's emergency use authorization of their vaccines in adults. Two reviewers (PD and RK) searched journal publications and trial data on the FDA's and Health Canada's websites to locate serious adverse event results tables for these trials. The Pfizer and Moderna trials are expected to follow participants for two years. Within weeks of the emergency authorization, however, the sponsors began a process of unblinding all participants who elected to be unblinded. In addition, those who received placebo were offered the vaccine. These self-selection processes may have introduced nonrandom differences between vaccinated and unvaccinated participants, thus rendering the post-authorization data less reliable. Therefore, to preserve randomization, we used the interim datasets that were the basis for emergency authorization in December 2020, approximately 4 months after trials commenced.

The definition of a serious adverse event (SAE) was provided in each trial's study protocol and included in the supplemental material of the trial's publication. [2–4] Pfizer and Moderna used nearly identical definitions, consistent with regulatory expectations. An SAE was defined as an adverse event that results in any of the following conditions: death; life-threatening at the time of the event; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; a congenital anomaly/birth defect; medically important event, based on medical judgment.

In addition to journal publications, we searched the websites of the FDA (for advisory committee meeting materials) and Health Canada (for sections of the dossier submitted by sponsors to the regulator). [5] For the FDA website, we considered presentations by both the FDA and the sponsors. [6] Within each of these sources, we searched for SAE results tables that presented information by specific SAE type; we chose the most recent SAE table corresponding to the FDA's requirement for a safety median follow-up time of at least 2 months after dose 2.

For each trial, we prepared blinded SAE tables (containing SAE types without results data). Using these blinded SAE tables, two clinician reviewers (JF and JE) independently judged whether each SAE type was an AESI. SAE types that matched an AESI term verbatim, or were an alternative diagnostic name for an AESI term, were included as an AESI. For all other SAE types, the reviewers independently judged whether that SAE type was likely to have been caused by a vaccine-induced AESI, based on a judgment considering the disease course, causative mechanism, and likelihood of the AESI to cause the SAE type. Disagreements were resolved through consensus; if consensus could not be reached, a third clinician reviewer (PW) was used to create a majority opinion. For each

included SAE, we recorded the corresponding Brighton Collaboration AESI category and organ system. When multiple AESIs could potentially cause the same SAE, the reviewers selected the AESI that they judged to be the most likely cause based on classical clinical presentation of the AESI.

We used an AESI list derived from the work of Brighton Collaboration's Safety Platform for Emergency vACcines (SPEAC) Project. This project created an AESI list which categorizes AESIs into three categories: those included because they are seen with COVID-19, those with a proven or theoretical association with vaccines in general, and those with proven or theoretical associations with specific vaccine platforms. The first version was produced in March 2020 based on experience from China. Following the second update (May 2020), the WHO Global Advisory Committee on Vaccine Safety (GACVS) adopted the list, and Brighton commenced a systematic review process "to ensure an ongoing understanding of the full spectrum of COVID-19 disease and modification of the AESI list accordingly." [7] This resulted in three additional AESIs being added to the list in December 2020. The subsequent (and most recent fourth) update did not result in any additional AESIs being added to the list. [1].

We matched SAEs recorded in the trial against an expanded list of AESIs created by combining Brighton's SPEAC COVID-19 AESI list with a list of 29 clinical diagnoses Brighton identified as "known to have been reported but not in sufficient numbers to merit inclusion on the AESI list." [7] Sensitivity analysis was used to determine whether use of the original versus expanded list altered our results.

Risk ratios and risk differences between vaccine and placebo groups were calculated for the incidence of AESIs and SAEs. We excluded SAEs that were known efficacy outcomes (i.e. COVID-19), consistent with the approach Pfizer (but not Moderna) used in recording SAE data. The Pfizer study trial protocol states that COVID-19 illnesses and their sequelae consistent with the clinical endpoint definition were not to be reported as adverse events, "even though the event may meet the definition of an SAE." [8] For unspecified reasons, Moderna included efficacy outcomes in their SAE tables, effectively reporting an all-cause SAE result. Because we did not have access to individual participant data, to account for the occasional multiple SAEs within single participants, we reduced the effective sample size by multiplying standard errors in the combined SAE analyses by the square root of the ratio of the number of SAEs to the number of patients with an SAE. This adjustment increased standard errors by 10 % (Pfizer) and 18 % (Moderna), thus expanding the interval estimates. We estimated combined risk ratios and risk differences for the two mRNA vaccines by averaging over the risks using logistic regression models which included indicators for trial and treatment group.

We used a simple harm-benefit framework to place our results in context, comparing risks of excess serious AESIs against reductions in COVID-19 hospitalization.

## 3. Results

Serious adverse event tables were located for each of the vaccine trials submitted for EUA in adults (age 16 + for Pfizer, 18 + for Moderna) in the United States: Pfizer-BioNTech COVID-19 vaccine BNT162b2 (NCT04368728) [2,9,10] and Moderna COVID-19 vaccine mRNA-1273 (NCT04470427). [3,11,12] (Table 1).

### 3.1. Reporting windows and serious adverse events

Moderna reported SAEs from dose 1 whereas Pfizer limited reporting from dose 1 to 1 month after dose 2. Both studies

**Table 1**
Data sources for phase III trials.

| Trial | Data cutoff date | Journal articles | FDA sources | Health Canada sources |
|---|---|---|---|---|
| Pfizer trial in ages 16 and above (NCT04368728) | 14 Nov 2020 (supported Dec 2020 EUA) | Aggregate data only | **Table 23 in sponsor briefing document** | **Table 55 in sponsor document C4591001 Final Analysis Interim Report Body** |
| Moderna trial in ages 18 and above (NCT04470427) | 25 Nov 2020 (supported Dec 2020 EUA) | Table S11 in publication | Table 27 in sponsor briefing document | **Table 14.3.1.13.3 in sponsor document mRNA-1273-P301 Unblinded Safety Tables Batch 1 (DS2)** |

Note: bolded font indicates dataset chosen for analysis; EUA = Emergency Use Authorization.

reported all data at the time of data cutoff (14 Nov 2020 for Pfizer, 25 Nov 2020 for Moderna). 17 SAEs that were efficacy endpoints were removed from the Moderna trial (16 "COVID-19" SAEs and 1 "COVID-19 pneumonia" SAE). One such efficacy endpoint meeting the definition of a SAE was removed from the Pfizer trial ("SARS-CoV-2 test positive" SAE).

The Pfizer trial exhibited a 36 % higher risk of serious adverse events in vaccinated participants in comparison to placebo recipients: 67.5 per 10,000 versus 49.5 per 10,000; risk difference 18.0 per 10,000 vaccinated participants (95 % compatibility[1] interval 1.2 to 34.9); risk ratio 1.36 (95 % CI 1.02 to 1.83). The Moderna trial exhibited a 6 % higher risk of SAEs in vaccinated individuals compared to those receiving placebo: 136 per 10,000 versus 129 per 10,000; risk difference 7.1 per 10,000 (95 % CI −23.2 to 37.4); risk ratio 1.06 (95 % CI 0.84 to 1.33). Combined, there was a 16 % higher risk of SAEs in mRNA vaccine recipients than placebo recipients: 98 per 10,000 versus 85 per 10,000; risk difference 13.2 (95 % CI −3.2 to 29.6); risk ratio 1.16 (95 % CI 0.97 to 1.39). (Table 2).

### 3.2. Serious adverse events of special interest

Regarding whether each SAE type was included on the SPEAC derived AESI list, agreement between the two independent clinician reviewers was 86 % (281/325); 40 of the 44 disagreements were resolved through consensus, and only four disagreements necessitated a third clinician reviewer. **Supplemental** Table 1 includes a full list of included and excluded SAEs across both trials.

In the Pfizer trial, 52 serious AESI (27.7 per 10,000) were reported in the vaccine group and 33 (17.6 per 10,000) in the placebo group. This difference corresponds to a 57 % higher risk of serious AESI (RR 1.57 95 % CI 0.98 to 2.54) and a risk difference of 10.1 serious AESI per 10,000 vaccinated participants (95 % CI −0.4 to 20.6). In the Moderna trial, 87 serious AESI (57.3 per 10,000) were reported in the vaccine group and 64 (42.2 per 10,000) in the placebo group. This difference corresponds to a 36 % higher risk of serious AESI (RR 1.36 95 % CI 0.93 to 1.99) and a risk difference of 15.1 serious AESI per 10,000 vaccinated participants (95 % CI −3.6 to 33.8). Combining the trials, there was a 43 % higher risk of serious AESI (RR 1.43; 95 % CI 1.07 to 1.92) and a risk difference of 12.5 serious AESI per 10,000 vaccinated participants (95 % CI 2.1 to 22.9). (Table 2).

Of the 236 serious AESIs occurring across the Pfizer and Moderna trials, 97 % (230/236) were adverse event types included as AESIs because they are seen with COVID-19. In both Pfizer and Moderna trials, the largest excess risk occurred amongst the Brighton category of coagulation disorders. Cardiac disorders have been of central concern for mRNA vaccines; in the Pfizer trial more cardiovascular AESIs occurred in the vaccine group than in the placebo group, but in the Moderna trial the groups differed by only 1 case. (Tables 3 and 4).

### 3.3. Sensitivity analysis

As a sensitivity analysis, we restricted the serious AESI analysis to those AESIs listed in SPEAC's COVID-19 AESI list (i.e. separating out Brighton's list of 29 clinical diagnoses "known to have been reported but not in sufficient numbers to merit inclusion on the AESI list.") This reduced the total number of AESIs across the two trials by 48 (35 vaccine group, 13 placebo group). There was still a higher risk of serious AESI when limited to the SPEAC COVID-19 AESI list, but the magnitude of the excess (in both relative and absolute terms) was smaller than when using the larger AESI list. **(Supplemental** Table 2).

### 3.4. Harm-benefit considerations

In the Moderna trial, the excess risk of serious AESIs (15.1 per 10,000 participants) was higher than the risk reduction for COVID-19 hospitalization relative to the placebo group (6.4 per 10,000 participants). [3] In the Pfizer trial, the excess risk of serious AESIs (10.1 per 10,000) was higher than the risk reduction for COVID-19 hospitalization relative to the placebo group (2.3 per 10,000 participants).

## 4. Comparison with FDA reviews

In their review of SAEs supporting the authorization of the Pfizer and Moderna vaccines, the FDA concluded that SAEs were, for Pfizer, "balanced between treatment groups," [15] and for Moderna, were "without meaningful imbalances between study arms." [16] In contrast to the FDA analysis, we found an excess risk of SAEs in the Pfizer trial. Our analysis of Moderna was compatible with FDA's analysis, finding no meaningful SAE imbalance between groups.

The difference in findings for the Pfizer trial, between our SAE analysis and the FDA's, may in part be explained by the fact that the FDA analyzed the total number of participants experiencing any SAE, whereas our analysis was based on the total number of SAE events. Given that approximately twice as many individuals in the vaccine group than in the placebo group experienced multiple SAEs (there were 24 more events than participants in the vaccine group, compared to 13 in the placebo group), FDA's analysis of only the incidence of participants experiencing any SAE would not reflect the observed excess of multiple SAEs in the vaccine group.

A more important factor, however, may be that FDA's review of non-fatal SAEs used a different analysis population with different follow-up windows. The FDA reported 126 of 21,621 (0.6 %) of vaccinated participants experienced at least one SAE at data cutoff compared to 111 of 21,631 (0.5 %) of placebo participants. In contrast, our analysis found 127 SAEs among 18,801 vaccine recipients versus 93 SAEs among 18,785 placebo recipients. [15] While summary results for the population we analyzed was provided in a table, FDA did not report an analysis of them. The substantially larger denominators in FDA's analysis (5,666 more participants) reflect the fact that their analysis included all individuals receiving at least one dose (minus 196 HIV-positive participants), irrespec-

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[1] A compatibility interval is identical to a confidence interval, but relabeled to emphasize that it is not a Bayesian posterior interval (as is improperly suggested by the "confidence" label).[13,14]

**Table 2**
Serious adverse events.

| Trial | Total events (events per 10,000 participants)[a] | | Risk difference per 10,000 participants (95 % CI)[e] | Risk ratio (95 % CI)[e] |
|---|---|---|---|---|
| | Vaccine | Placebo | | |
| **Serious adverse events** | | | | |
| Pfizer[b] | 127 (67.5) | 93 (49.5) | 18.0 (1.2 to 34.9) | 1.36 (1.02 to 1.83) |
| Moderna[c,d] | 206 (135.7) | 195 (128.6) | 7.1 (−23.2 to 37.4) | 1.06 (0.84 to 1.33) |
| Combined[f] | 333 (98.0) | 288 (84.8) | 13.2 (-3.2 to 29.6) | 1.16 (0.97 to 1.39) |
| **Serious adverse events of special interest** | | | | |
| Pfizer | 52 (27.7) | 33 (17.6) | 10.1 (-0.4 to 20.6) | 1.57 (0.98 to 2.54) |
| Moderna | 87 (57.3) | 64 (42.2) | 15.1 (-3.6 to 33.8) | 1.36 (0.93 to 1.99) |
| Combined[f] | 139 (40.9) | 97 (28.6) | 12.5 (2.1 to 22.9) | 1.43 (1.07 to 1.92) |

[a] Denominators for Pfizer were 18,801 in the vaccine group and 18,785 in the placebo group, and for Moderna were 15,185 in the vaccine group and 15,166 in the placebo group.

[b] Pfizer excluded efficacy outcomes from its SAE table (COVID-19 illnesses and their sequelae meeting the definition of an SAE). However, at least one SAE appears to have been inadvertently included, which we removed from our calculations ("SARS-CoV-2 test positive": 0 vaccine group; 1 placebo group).

[c] Moderna included efficacy outcomes in its SAE table (COVID-19 illnesses and their sequelae meeting the definition of an SAE). We removed efficacy SAEs outcomes that could be identified: "COVID-19" and "COVID-19 pneumonia." Lacking access to participant level data, SAEs that were sequelae of serious COVID-19 could not be identified and therefore remain included in this analysis.

[d] "All SAEs" for Moderna was calculated using the "Number of serious AEs" row in Moderna's submission to FDA.[11]

[e] Standard errors used to estimate 95% CIs were inflated by the factor $\sqrt{[\#SAE]/[\#patients\ with\ SAE]}$ to account for multiple SAE within patients.

[f] The combined risk differences and risk ratios were computed from the fitted logistic regression models and so may not exactly equal comparisons computed from the first two columns.

**Table 3**
Serious AESIs, Pfizer trial.

| Brighton category | Vaccine | Placebo | Vaccine events per 10,000 | Placebo events per 10,000 | Difference in events per 10,000 | Risk ratio |
|---|---|---|---|---|---|---|
| **Association with immunization in general** | | | | | | |
| Anaphylaxis | 1 | 1 | 0.5 | 0.5 | 0.0 | 1.00 |
| **Association with specific vaccine platform(s)** | | | | | | |
| Encephalitis/encephalomyelitis | 0 | 2 | 0.0 | 1.1 | −1.1 | 0.00 |
| **Seen with COVID-19** | | | | | | |
| Acute kidney injury | 2 | 0 | 1.1 | 0.0 | 1.1 | N/A |
| Acute liver injury | 0 | 1 | 0.0 | 0.5 | −0.5 | 0.00 |
| Acute respiratory distress syndrome | 2 | 1 | 1.1 | 0.5 | 0.5 | 2.00 |
| Coagulation disorder | 16 | 10 | 8.5 | 5.3 | 3.2 | 1.60 |
| Myocarditis/pericarditis | 2 | 1 | 1.1 | 0.5 | 0.5 | 2.00 |
| Other forms of acute cardiac injury | 16 | 12 | 8.5 | 6.4 | 2.1 | 1.33 |
| Subtotal | 39 | 28 | 20.7 | 14.9 | 5.8 | 1.39 |
| **Brighton list of 29 clinical diagnoses seen with COVID-19** | | | | | | |
| Abscess | 4 | 1 | 2.1 | 0.5 | 1.6 | 4.00 |
| Cholecystitis | 4 | 2 | 2.1 | 1.1 | 1.1 | 2.00 |
| Colitis/Enteritis | 1 | 1 | 0.5 | 0.5 | 0.0 | 1.00 |
| Diarrhea | 1 | 0 | 0.5 | 0.0 | 0.5 | N/A |
| Hyperglycemia | 1 | 1 | 0.5 | 0.5 | 0.0 | 1.00 |
| Pancreatitis | 1 | 0 | 0.5 | 0.0 | 0.5 | N/A |
| Psychosis | 1 | 0 | 0.5 | 0.0 | 0.5 | N/A |
| Subtotal | 13 | 5 | 6.9 | 2.7 | 4.3 | 2.60 |
| **Total** | **52** | **33** | **27.7** | **17.6** | **10.1** | **1.57** |

tive of the duration of post-injection follow-up time. In contrast, our analysis was based on the study population with median follow-up ≥ 2 months after dose 2 (minus 120 HIV-positive participants), of which 98.1 % had received both doses. [2,17] The FDA's analysis of SAEs thus included thousands of additional participants with very little follow-up, of which the large majority had only received 1 dose.

### 4.1. Comparison with post-authorization studies

Although the randomized trials offer high level evidence for evaluating causal effects, the sparsity of their data necessitates that harm-benefit analyses also consider observational studies. Since their emergency authorization in December 2020, hundreds of millions of doses of Pfizer and Moderna COVID-19 vaccines have been administered and post-authorization observational data offer a complementary opportunity to study AESIs. Post-authorization observational safety studies include cohort studies (which make use of medical claims or electronic health records) and dispropor-

tionality analyses (which use spontaneous adverse event reporting systems). In July 2021, the FDA reported detecting four potential adverse events of interest: pulmonary embolism, acute myocardial infarction, immune thrombocytopenia, and disseminated intravascular coagulation following Pfizer's vaccine based on medical claims data in older Americans. [18] Three of these four serious adverse event types would be categorized as coagulation disorders, which is the Brighton AESI category that exhibited the largest excess risk in the vaccine group in both the Pfizer and Moderna trials. FDA stated it would further investigate the findings but at the time of our writing has not issued an update. Similarly, spontaneous-reporting systems have registered serious adverse reactions including anaphylaxis (all COVID-19 vaccines), thrombocytopenia syndrome among premenopausal females (Janssen vaccine), and myocarditis and pericarditis among younger males (Pfizer and Moderna vaccines). [19,20].

Using data from three postmarketing safety databases for vaccines (VAERS, EudraVigilance, and VigiBase), disproportionality studies have reported excess risks for many of the same SAE types as in

**Table 4**
Serious AESIs, Moderna trial.

| Brighton category | Vaccine | Placebo | Vaccine events per 10,000 | Placebo events per 10,000 | Difference in events per 10,000 | Risk ratio |
|---|---|---|---|---|---|---|
| **Association with specific vaccine platform(s)** | | | | | | |
| Bell's Palsy | 1 | 0 | 0.7 | 0.0 | 0.7 | N/A |
| Encephalitis/encephalomyelitis | 1 | 0 | 0.7 | 0.0 | 0.7 | N/A |
| **Seen with COVID-19** | | | | | | |
| Acute kidney injury | 1 | 3 | 0.7 | 2.0 | −1.3 | 0.33 |
| Acute liver injury | 1 | 0 | 0.7 | 0.0 | 0.7 | N/A |
| Acute respiratory distress syndrome | 7 | 4 | 4.6 | 2.6 | 2.0 | 1.75 |
| Angioedema | 0 | 2 | 0.0 | 1.3 | −1.3 | 0.00 |
| Coagulation disorder | 20 | 13 | 13.2 | 8.6 | 4.6 | 1.54 |
| Generalized Convulsions | 2 | 0 | 1.3 | 0.0 | 1.3 | N/A |
| Myelitis | 0 | 1 | 0.0 | 0.7 | −0.7 | 0.00 |
| Myocarditis/pericarditis | 4 | 5 | 2.6 | 3.3 | −0.7 | 0.80 |
| Other forms of acute cardiac injury | 26 | 26 | 17.1 | 17.1 | 0.0 | 1.00 |
| Other rash | 1 | 1 | 0.7 | 0.7 | 0.0 | 1.00 |
| Rhabdomyolysis | 0 | 1 | 0.0 | 0.7 | −0.7 | 0.00 |
| Single Organ Cutaneous Vasculitis | 1 | 0 | 0.7 | 0.0 | 0.7 | N/A |
| Subtotal | 65 | 56 | 42.8 | 36.9 | 5.9 | 1.16 |
| **Brighton list of 29 clinical diagnoses seen with COVID-19** | | | | | | |
| Abscess | 1 | 0 | 0.7 | 0.0 | 0.7 | N/A |
| Arthritis | 3 | 1 | 2.0 | 0.7 | 1.3 | 3.00 |
| Cholecystitis | 4 | 0 | 2.6 | 0.0 | 2.6 | N/A |
| Colitis/Enteritis | 6 | 3 | 4.0 | 2.0 | 2.0 | 2.00 |
| Diarrhea | 2 | 1 | 1.3 | 0.7 | 0.7 | 2.00 |
| Hyperglycemia | 1 | 0 | 0.7 | 0.0 | 0.7 | N/A |
| Hyponatremia | 1 | 1 | 0.7 | 0.7 | 0.0 | 1.00 |
| Pancreatitis | 2 | 0 | 1.3 | 0.0 | 1.3 | N/A |
| Pneumothorax | 0 | 1 | 0.0 | 0.7 | −0.7 | 0.00 |
| Psychosis | 1 | 1 | 0.7 | 0.7 | 0.0 | 1.00 |
| Thyroiditis | 1 | 0 | 0.7 | 0.0 | 0.7 | N/A |
| Subtotal | 22 | 8 | 14.5 | 5.3 | 9.2 | 2.75 |
| **Total** | **87** | **64** | **57.3** | **42.2** | **15.1** | **1.36** |

the present study. [21–23] For example, a study using VAERS and EudraVigilance comparing the disproportionality of adverse event reports between the influenza vaccine versus the mRNA COVID-19 vaccines reported excess risks for the following Brighton AESIs: cardiovascular events, coagulation events, hemorrhages, gastrointestinal events, and thromboses. [22] While CDC published a protocol[24] in early 2021 for using proportional reporting ratios for signal detection in the VAERS database, results from the study have not yet been reported. [25] Among self-controlled case series, one reported a rate ratio of 1.38 (95 % CI 1.12–1.71) for hemorrhagic stroke following Pfizer vaccine, [26] another reported 0.97 (95 % CI 0.81–1.15), [27] while a cohort study[28] reported 0.84 (95 % CI 0.54–1.27).

## 5. Discussion

Using a prespecified list of AESI identified by the Brighton Collaboration, higher risk of serious AESI was observed in the mRNA COVID-19 vaccine group relative to placebo in both the Pfizer and Moderna adult phase III trials, with 10.1 (Pfizer) and 15.1 (Moderna) additional events for every 10,000 individuals vaccinated. Combined, there was a risk difference of 12.5 serious AESIs per 10,000 individuals vaccinated (95 % CI 2.1 to 22.9). These results raise concerns that mRNA vaccines are associated with more harm than initially estimated at the time of emergency authorization. In addition, our analysis identified a 36 % higher risk of serious adverse events in vaccinated participants in the Pfizer trial: 18.0 additional SAEs per 10,000 vaccinated (95 % CI 1.2 to 34.9). Consistent with the FDA evaluation, our analysis found no clear difference in SAEs between groups in the Moderna trial.

Results between the Pfizer and Moderna trials were similar for the AESI analysis but exhibited substantial variation in the SAE analysis. Caution is needed in interpreting this variation as it may be substantially explained by differences in SAE recording

practices in the trials rather than differences in actual vaccine harm profiles. For reasons that are not documented in the trial protocol, Moderna included efficacy outcomes in its SAE tabulations, while Pfizer excluded them. As a result, Moderna's SAE table did not present a traditional SAE analysis but rather an all-cause SAE analysis. The FDA analysis of the Moderna trial presented an all-cause SAE analysis, which estimates total vaccine effects on SAEs, including effects transmitted via effects on COVID-19. It did not however present a traditional SAE analysis with efficacy endpoints removed, which attempts to estimate only the direct effects on SAEs. While our analysis attempted to perform a traditional SAE analysis by excluding efficacy SAEs (serious COVID-19 and its sequelae), our effort was hindered because we did not have access to patient level data. Easily recognizable efficacy SAEs ("COVID-19", "COVID-19 pneumonia," and "SARS-CoV-2 test positive") could be removed, but many participants who experienced a COVID-19 SAE likely experienced multiple other SAEs (e.g. pneumonia, hypoxia, and thrombotic events) which could not be identified and therefore remain included in our analysis. Of 17 total efficacy SAEs (16 "COVID-19" and 1 "COVID-19 pneumonia") removed from our analysis of the Moderna trial, 16 were in the placebo arm. As a consequence, the background SAE risk (risk in absence of COVID-19) would be overestimated by the Moderna placebo group, resulting in underestimation of the actual risk of SAEs and AESIs attributable to the vaccine in the Moderna comparisons as well as in the combined analysis. Access to patient-level data would allow adjustments for this problem.

Rational policy formation should consider potential harms alongside potential benefits. [29] To illustrate this need in the present context, we conducted a simple harm-benefit comparison using the trial data comparing excess risk of serious AESI against reductions in COVID-19 hospitalization. We found excess risk of serious AESIs to exceed the reduction in COVID-19 hospitalizations in both Pfizer and Moderna trials.

This analysis has the limitations inherent in most harm-benefit comparisons. First, benefits and harms are rarely exact equivalents, and there can be great variability in the degree of severity within both benefit and harm endpoints. For example, intubation and short hospital stay are not equivalent but both are counted in "hospitalization"; similarly, serious diarrhea and serious stroke are not equivalent but both are counted in "SAE." Second, individuals value different endpoints differently. Third, without individual participant data, we could only compare the number of individuals hospitalized for COVID-19 against the number of serious AESI events, not the number of participants experiencing any serious AESI. Some individuals experienced multiple SAEs whereas hospitalized COVID-19 participants were likely only hospitalized once, biasing the analysis towards exhibiting net harm. To gauge the extent of this bias, we considered that there were 20 % (Pfizer) and 34 % (Moderna) more SAEs than participants experiencing any SAE. As a rough sensitivity calculation, if we divide the Pfizer excess serious AESI risk of 10.1 by 1.20 it becomes 8.4 compared to a COVID-19 hospitalization risk reduction of 2.3; if we divide the Moderna excess serious AESI risk of 15.1 by 1.34 it becomes 11.3 compared to a COVID-19 hospitalization risk reduction of 6.4.

Harm-benefit ratios will be different for populations at different risk for serious COVID-19 and observation periods that differ from those studied in the trials. Presumably, larger reductions in COVID-19 hospitalizations would have been recorded if trial follow-up were longer, more SARS-CoV-2 was circulating, or if participants had been at higher risk of serious COVID-19 outcomes, shifting harm-benefit ratios toward benefit. Conversely, harm-benefit ratios would presumably shift towards harm for those with lower risk of serious COVID-19 outcomes--such as those with natural immunity, younger age or no comorbidities. Similarly, waning vaccine effectiveness, decreased viral virulence, and increasing degree of immune escape from vaccines might further shift the harm-benefit ratio toward harm. Large, randomized trials in contemporary populations could robustly answer these questions. Absent definitive trials, however, synthesis of multiple lines of evidence will be essential. [30,48,49].

Adverse events detected in the post-marketing period have led to the withdrawal of several vaccines. An example is intussusception following one brand of rotavirus vaccine: around 1 million children were vaccinated before identification of intussusception, which occurred in around 1 per 10,000 vaccinees. [31] Despite the unprecedented scale of COVID-19 vaccine administration, the AESI types identified in our study may still be challenging to detect with observational methods. Most observational analyses are based on comparing the risks of adverse events "observed" against a background (or "expected") risk, which inevitably display great variation, by database, age group, and sex. [32] If the actual risk ratio for the effect was 1.4 (the risk ratio of the combined AESI analysis), it could be quite difficult to unambiguously replicate it with observational data given concerns about systematic as well as random errors. [33–35].

In addition, disproportionality analyses following COVID-19 vaccination also have limitations, particularly with respect to the type of adverse events seen in our study. The majority of SAEs that contributed to our results are relatively common events, such as ischemic stroke, acute coronary syndrome, and brain hemorrhage. This complicates signal detection because clinical suspicion of an adverse vaccine reaction following an event commonly seen in clinical practice will be lower than for SAEs like myocarditis.[50] For this reason, clinical suspicion leading to the filing of an individual case safety report--may be far less common in the post-authorization setting than in the trials. At the same time, heightened awareness about COVID-19 vaccine SAEs can result in under and overreporting. Public health messages assuring vaccine safety may lower clinical suspicion of potential causal relationships, whereas messages about potential harms can conversely stimulate reports that otherwise may not have been made. These factors can lead to bias both directions, further complicating interpretation. In contrast to these problems, in the randomized trials used in this analysis, all SAEs were to be recorded, irrespective of clinical judgment regarding potential causality.

Although our analysis is secondary, reanalyses of clinical trial data have led to the detection of adverse events well after the market entry of major drugs such as rofecoxib and rosiglitazone. [36,37] Our analysis has an advantage over postmarketing observational studies in that the data are from blinded, placebo-controlled randomized trials vetted by the FDA, which were matched against a list of adverse events created before the availability of the clinical-trial results and designed for use in COVID-19 vaccine trials.

Our study has several important limitations. First, Pfizer's trial did not report SAEs occurring past 1 month after dose 2. This reporting threshold may have led to an undercounting of serious AESIs in the Pfizer trial. Second, for both studies, the limited follow up time prevented an analysis of harm-benefit over a longer period. Third, all SAEs in our analysis met the regulatory definition of a serious adverse event, but many adverse event types which a patient may themselves judge as serious may not meet this regulatory threshold. Fourth, decisions about which SAEs to include or exclude as AESIs requires subjective, clinical judgements in the absence of detailed clinical information about the actual SAEs. We encourage third party replication of our study, with access to complete SAE case narratives, to determine the degree to which these decisions affected our findings. For additional sensitivity analyses, such replication studies could also make use of other AESI lists, such as those prepared by FDA, [38–41] CDC, [24], Pfizer, [42], or a *de novo* AESI list derived from a list of COVID-19 complications understood to be induced via SARS-CoV-2′s spike protein. [43,44].

A fifth important limitation is our lack of access to individual participant data, which forced us to use a conservative adjustment to the standard errors. The 95 % CIs[13,14] calculated are therefore only approximate because we do not know which patients had multiple events. Finally, as described above, in the Moderna analysis, the SAEs that were sequelae of serious COVID-19 could not be identified and therefore remain included in our calculations. Because the vaccines prevent SAEs from COVID-19 while adding SAE risks of their own, this inclusion makes it impossible to separately estimate SAEs due to the vaccine from SAEs due to COVID-19 in the available Moderna data, as must be done to extrapolate harm-benefit to other populations. These study limitations all stem from the fact that the raw data from COVID-19 vaccine clinical trials are not publicly available. [45,46].

We emphasize that our investigation is preliminary, to point to the need for more involved analysis. The risks of serious AESIs in the trials represent only group averages. SAEs are unlikely to be distributed equally across the demographic subgroups enrolled in the trial, and the risks may be substantially less in some groups compared to others. Thus, knowing the actual demographics of those who experienced an increase in serious AESI in the vaccine group is necessary for a proper harm-benefit analysis. In addition, clinical studies are needed to see if particular SAEs can be linked to particular vaccine ingredients as opposed to unavoidable consequences of exposure to spike protein, as future vaccines could then be modified accordingly or sensitivities can be tested for in advance. In parallel, a systematic review and meta-analysis using individual participant data should be undertaken to address questions of harm-benefit in various demographic subgroups, particularly in those at low risk of serious complications from COVID-19. Finally, there is a pressing need for comparison of SAEs and harm-benefit for different vaccine types; some initial work has already begun in this direction. [47].

Full transparency of the COVID-19 vaccine clinical trial data is needed to properly evaluate these questions. Unfortunately, as we approach 2 years after release of COVID-19 vaccines, participant level data remain inaccessible. [45,46].

## Author contributions

All authors had full access to all of the data in the study (available at https://doi.org/10.5281/zenodo.6564402), and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.
Acquisition of data: Doshi.
Analysis and interpretation: All authors.
Statistical analysis: Jones, Greenland.
Drafting of the manuscript: Fraiman, Doshi.
Critical revision of the manuscript for important intellectual content: All authors.

## Data availability

All of the data in the study is available at https://doi.org/10.5281/zenodo.6564402

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Ethical review statement

This research was confirmed to be Not Human Subjects Research (NHSR) by University of Maryland, Baltimore (HP-00102561).

## Conflicts of interest

JF, JE, MJ, SG, PW, RK: none to declare. PD has received travel funds from the European Respiratory Society (2012) and Uppsala Monitoring Center (2018); grants from the FDA (through University of Maryland M-CERSI; 2020), Laura and John Arnold Foundation (2017-22), American Association of Colleges of Pharmacy (2015), Patient-Centered Outcomes Research Institute (2014-16), Cochrane Methods Innovations Fund (2016-18), and UK National Institute for Health Research (2011-14); was an unpaid IMEDS steering committee member at the Reagan-Udall Foundation for the FDA (2016-2020) and is an editor at The BMJ. The views expressed here are those of the authors and do not necessarily reflect those of their employers.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.08.036.

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